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Respiratory Health Effects of Passive Smoking:

Review Draft

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Lung Cancer and Other Disorders

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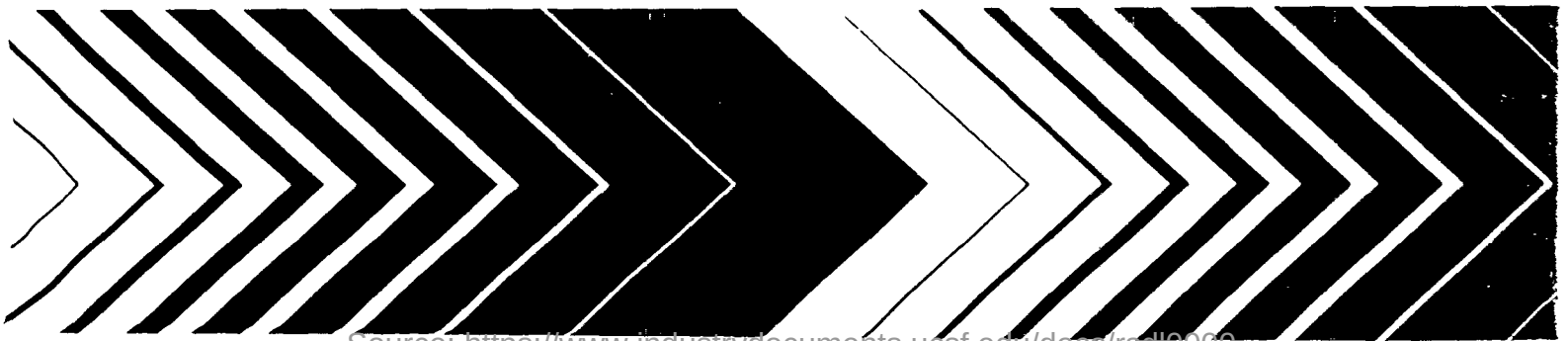

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RESPIRATORY HEALTH EFFECTS OF PASSIVE SMOKING: LUNG CANCER AND OTHER DISORDERS

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U.S. Environmental Protection Agency
Washington, D.C.

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PREFACE

This assessment of the respiratory health effects associated with passive smoking has been prepared by the Human Health Assessment Group, Office of Health and Environmental Assessment, Office of Research and Development, which is responsible for its scientific accuracy and conclusions. The assessment was prepared at the request of the Indoor Air Division, Office of Atmospheric and Indoor Air Programs, Office of Air and Radiation, which defined its scope and provided funding.

The document has been developed under the authority of Title IV of Superfund (The Radon Gas and Indoor Air Quality Research Act of 1986) to provide information and guidance on the potential hazards of indoor air pollutants.

An earlier draft of this document was made available for public review and comments in June 1990, and was reviewed by the Agency's Science Advisory Board in December 1990. This revision reflects the comments received from those reviews, plus additional comments from an internal review conducted in February and March 1992.

A comprehensive search of the scientific literature for this revision is complete through September 1991. In addition, a few studies published since then have been included in response to recommendations made by reviewers.

Due to both resource and time constraints, the scope of this report has been limited to an analysis of respiratory effects, primarily lung cancer in nonsmoking adults and noncancer respiratory illnesses in children, with emphasis on the epidemiologic data. Further, because two thorough reviews on passive smoking were completed in 1986 (by the U.S. Surgeon General and the National Research Council), this document provides a summary of those reports with a more comprehensive analysis of the literature appearing subsequent to those reports and an integration of the results.

It is the Agency's intention with the release of this draft to seek additional advice from its Science Advisory Board in preparation for release of a final report later this year.

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AUTHORS, CONTRIBUTORS, AND REVIEWERS

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Other OHEA staff responsible for the scientific content of sections of this document are Aparna M. Koppikar[1] and Jennifer Jinot[1]. Jennifer Jinot also served as a contributor and technical editor for a major portion of this report.

AUTHORS

Major portions of this revised report were prepared by ICF Incorporated, Fairfax, Virginia, under EPA Contract No. 68-00-0102. A list of authors follows:

Chapter 1:	Steven P. Bayard[1]
Chapter 2:	Jennifer Jinot[1]
Chapter 3:	Brian P. Leaderer[2]
Chapter 4:	Jennifer Jinot
Chapters 5/6:	Kenneth G. Brown[3]

[1]Human Health Assessment Group, Office of Health and Environmental Assessment, U.S. EPA, Washington, DC 20460.

[2]J. P. Pierce Foundation Laboratory, Department of Epidemiology and Public Health, Yale University School of Medicine, New Haven, CT 06520. Subcontractor to ICF Inc.

[3]Kenneth G. Brown, Inc., P. O. Box 16608, Chapel Hill, NC 27516. Subcontractor to ICF Inc.

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Chapters 7:	Fernando D. Martinez[4]
Chapters 8:	Fernando D. Martinez and Steven P. Bayard
Appendix A:	Kenneth G. Brown, Neal R. Simonsen[3], and A. Judson Wells[3]
Appendix B:	A. Judson Wells
Appendix C:	Kenneth G. Brown
Appendix D:	Kenneth G. Brown and Neal R. Simonsen
Appendix E:	Kenneth G. Brown

CONTRIBUTORS

Numerous persons have provided helpful discussions or responded to requests for pre-prints, data, and other material relevant to this report. The authors are grateful to W.J. Blot, N. Britten, R.C. Brownson, P.A. Buffler, T.L. Butler, D.B. Coultas, K.M. Cummings, J. Fleiss, E.T.H. Fontham, Y.T. Gao, L. Garfinkel, S. Glantz, N.J. Haley, T. Hirayama, D.J. Hole, C. Humble, G.C. Kabat, J.C. Kleinman, L.C. Koo, M. Layard, P.N. Lee, M.D. Lebowitz, P. Macaskill, G.J. Knight, G.E. Palomaki, J.P. Pierce, J. Repace, H. Shimizu, W.F. Stewart, D. Trichopoulos, A. Wu-Williams, and R.W. Wilson.

---

[3]Kenneth G. Brown, Inc., P. O. Box 16608, Chapel Hill, NC 27516. Subcontractor to ICF Inc.

[4]Division of Respiratory Sciences, University of Arizona Medical Center, Tucson, AZ 85724. Subcontractor to ICF Inc.

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REVIEWERS

This document is a revision of an earlier External Review Draft (EPA/600/6-90/006A) that was released for public review and comment on June 25, 1990. The draft document subsequently was reviewed by the EPA Science Advisory Board (SAB) on December 4 and 5, 1990. Many of the revisions follow closely the valuable advice presented in the SAB's April 19, 1991, report to the Agency. Other revisions are based on comments received from peer reviewers and the public. In addition, many reviewers both within and outside the Agency provided assistance at various internal review stages.

The following members of the SAB's Indoor Air Quality and Total Human Exposure Committee (IAQTHEC) participated in the review of the External Review Draft.

Chairman

Dr. Morton Lippmann, Professor, Institute of Environmental Medicine, New York University Medical Center, Tuxedo, NY 10987

Vice Chairman

Dr. Jan A.J. Stolwijk, Professor, School of Medicine, Department of Epidemiology and Public Health, Yale University, 60 College Street, New Haven, CT 06510

Members of the IAQTHEC

Dr. Joan Daisey, Senioor Scientist, Indoor Environment Program, Lawrence Berkeley Laboratory, One Cyclotron Road, Berkeley, CA 94720

Dr. Victor G. Laties, Professor of Toxicology, Environmental Health Science Center-Box EHSC, University of Rochester School of Medicine, Rochester, NY 14642

Dr. Jonathan M. Samet, Professor of Medicine, Department of Medicine; The Univeristy of New Mexico School of Medicine, and The New Mexico Tumor Registry, 900 Camino De Salud, NE, Albuquerque, NM 87131

Dr. Jerome J. Wesolowski, Chief, Air and Industrial Hygiene Laboratory, California Department of Health, Berkeley, CA 94704

Dr. James E. Woods, Jr., Professor of Building Construction, College of Architecture and Urban Studies, 117 Burress Hall, Virginia Polytechnic Institute and State University, Blacksburg, VA 24061-0156

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Consultants to the IAQTHEC

Dr. Neal L. Benowitz, Professor of Medicine, Chief, Division of Clinical Pharmacology and Experimental Therapeutics, University of California, San Francisco, Building 30, Fifth Floor, San Francisco General Hospital, 1001 Potrero Avenue, San Francisco, CA 94110

Dr. William J. Blot, National Cancer Institute, 9000 Rockville Pike, Bethesda, MD 20892 (Federal Liaison to the Committee)

Dr. David Burns, Associate Professor of Medicine, Department of Medicine, University of California, San Diego Medical Center, 225 Dickenson Street, San Diego, CA 92103-1990

Dr. Delbert Eatough, Professor of Chemistry, Brigham Young University, Provo, UT 84602

Dr. S. Katharine Hammond, Associate Professor, Environmental Health Sciences Program, Department of Family and Community Medicine, University of Massachusetts Medical School, 55 Lake Avenue, North, Worcester, MA 06155

Dr. Geoffrey Kabat, Senior Epidemiologist, American Health Foundation, 320 East 43rd Street, New York, NY 10017

Dr. Michael D. Lebowitz, Professor of Internal Medicine, University of Arizona College of Medicine, Division of Respiratory Sciences, Tucson, AZ 85724

Dr. Howard Rockette, Professor of Biostatistics, School of Public Health, 318 Parran Hall, University of Pittsburgh, Pittsburgh, PA 15261

Dr. Scott T. Weiss, Channing Laboratory, Harvard University School of Medicine, Boston, MA 02115

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1. SUMMARY AND CONCLUSIONS

1.1. BACKGROUND

Tobacco smoking has long been recognized (e.g., U.S. DHEW, 1964) as a major cause of mortality and morbidity, responsible for an estimated 434,000 deaths per year in the United States (CDC, 1991a). Tobacco use is known to cause cancer at various sites, in particular the lung (U.S. DHHS, 1982; IARC, 1986). Smoking can also cause respiratory diseases (U.S. DHHS, 1984, 1989) and is a major risk factor for heart disease (U.S. DHHS, 1983). In recent years there has been concern that nonsmokers may also be at risk for some of these health effects as a result of their exposure ("passive smoking") to the tobacco smoke that occurs in various environments occupied by smokers. Although this environmental tobacco smoke (ETS) is dilute compared to the mainstream smoke (MS) inhaled by active smokers, it is chemically similar, containing many of the same carcinogenic and toxic agents.

In 1986, the National Research Council (NRC) and the Surgeon General of the U.S. Public Health Service independently assessed the health effects of exposure to ETS (NRC, 1986; U.S. DHHS, 1986). Both of the 1986 reports conclude that ETS can cause lung cancer in adult nonsmokers and that children of parents who smoke have increased frequency of respiratory symptoms and acute lower respiratory tract infections, as well as evidence of reduced lung function.

More recent epidemiologic studies of the potential associations between ETS and lung cancer in nonsmoking adults and between ETS and noncancer respiratory effects more than double the size of the database available for analysis from that of the 1986 reports. This U.S. EPA document critically reviews the current database on the respiratory health effects of passive smoking, and these data are utilized to develop a hazard identification for ETS and to make quantitative estimates of the public health impacts of ETS for lung cancer and various other respiratory diseases.

The weight-of-evidence analysis for the lung cancer hazard identification is developed in accordance with U.S. EPA's *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 1986a) and established principles for evaluating epidemiologic studies. The analysis considers animal bioassays and genotoxicity studies, as well as biological measurements of human uptake of tobacco smoke components and epidemiologic data on active and passive smoking. The availability of abundant and consistent human data, and especially human data at actual environmental levels of exposure to the specific agent (mixture) of concern, allow a hazard identification to be made with

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a high degree of certainty. The conclusive evidence of the dose-related lung carcinogenicity of MS in active smokers (Chapter 4), coupled with information on the chemical similarities of MS and ETS and evidence of ETS uptake in nonsmokers (Chapter 3), is sufficient by itself to establish ETS as a known human lung carcinogen, or "Group A" carcinogen under U.S. EPA's carcinogen classification system. In addition, this document concludes that the overall results of 30 epidemiologic studies on lung cancer and passive smoking (Chapter 3), using spousal smoking as a surrogate of ETS exposure for female never-smokers, similarly justify a Group A classification.

The weight-of-evidence analyses for the noncancer respiratory effects are based primarily on a review of epidemiologic studies (Chapter 7). Most of the endpoints examined are respiratory disorders in children, where parental smoking is used as a surrogate of ETS exposure. For the noncancer respiratory effects in nonsmoking adults, most studies used spousal smoking as an exposure surrogate. A causal association was concluded to exist for a number of respiratory disorders where there was sufficient consistent evidence for a biologically-plausible association with ETS that could not be explained by bias, confounding, or chance. The fact that the database consists of human evidence from actual environmental exposure levels gives a high degree of confidence in this conclusion. Where there was suggestive but inconclusive evidence of causality, as was the case for asthma induction in children, ETS was concluded to be a risk factor for that endpoint. Where data were inconsistent or inadequate for evaluation of an association, as for acute upper respiratory tract infections and acute middle ear infections in children, no conclusions were drawn.

This report has also attempted to provide estimates of the extent of the public health impact, where appropriate, in terms of numbers of ETS-attributable cases in nonsmoking subpopulations. Unlike for qualitative hazard identification assessments where information from many sources adds to the confidence in a weight-of-evidence conclusion, for quantitative risk assessments the usefulness of studies usually depends on how closely the study population resembles nonsmoking segments of the general population. For lung cancer estimates among U.S. nonsmokers, the substantial epidemiology database of ETS and lung cancer among U.S. female never-smokers was considered to provide the most appropriate information. From the large number of similarly designed studies, pooled relative risk estimates were calculated and used in the derivation of the population risk estimates. The large number of studies available, the generally consistent results, and the condition of actual environmental levels of exposure increase the confidence in these estimates. Even with these conditions, however, uncertainties remain, such as in the use of questionnaires and current biomarker measurements to estimate past

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exposure, assumptions of exposure-response linearity, and extrapolation to male never-smokers and to exsmokers. Still, given the strength of the evidence for the lung carcinogenicity of tobacco smoke and the extensive human database from actual environmental exposure levels, fewer assumptions are necessary than is usual in U.S. EPA quantitative risk assessments and confidence in these estimates is rated medium to high.

Population estimates of ETS health impacts are also made for certain noncancer respiratory endpoints in children, specifically lower respiratory tract infections (LRIs, i.e. pneumonia, bronchitis, and bronchiolitis) and episodes and severity of attacks of asthma. Estimates of ETS-attributable cases of LRI in infants and young children are thought to have a high degree of confidence because of the consistent study findings and the appropriateness of parental smoking as a surrogate measure of exposure in very young children. Estimates of the number of asthmatic children whose condition is aggravated by exposure to ETS are less certain than those for LRIs because of different measures of outcome in various studies and because of increased extraparental exposure to ETS in older children. Estimates of the number of new cases of asthma in previously asymptomatic children also have less confidence because at this time the weight-of-evidence for asthma induction, while suggestive of a causal association, is not conclusive.

Most of the ETS population impact estimates are presented in terms of ranges, which are thought to reflect reasonable assumptions about the estimates of parameters and variables required for the extrapolation models. The validity of the ranges is also dependent on the appropriateness of the extrapolation models themselves.

While this report focuses only on the respiratory health effects of passive smoking, there may also be other health effects of concern. Recent analyses of more than a dozen epidemiology and toxicology studies (Steenland, 1992; NIOSH, 1991) suggest that ETS exposure may be a risk factor for cardiovascular disease. In addition, there were a few studies in the literature linking ETS exposure to cancers of others sites; at this time, that database appears inadequate for any conclusion. This report does not develop an analysis of either the nonrespiratory cancer or the heart disease data and takes no position on whether ETS is a risk factor for these diseases. If it is, the total public health impact from ETS will be greater than that discussed here.

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1.2. PRIMARY FINDINGS

A. Lung Cancer in Nonsmoking Adults

1. Passive smoking is causally associated with lung cancer in adults, and ETS, by the total weight-of-evidence, belongs in the category of compounds classified by EPA as Group A (known human) carcinogens.
2. An estimated range of 2,500 to 3,300 lung cancer deaths per year among nonsmokers (never-smokers and former smokers) of both sexes are attributable to ETS in the United States. The confidence in this range is medium to high with approximately 3,000 annual lung cancer deaths representing the best estimate.

B. Noncancer Respiratory Diseases and Disorders

1. Exposure of children to ETS from parental smoking is causally associated with:
   a. increased prevalence of respiratory symptoms of irritation (cough, sputum, and wheeze),
   b. increased prevalence of middle ear effusion (a sign of middle ear disease), and
   c. a small but statistically significant reduction in lung function as tested by objective measures of lung capacity.
2. ETS exposure of young children and particularly infants from parental (and especially mother's) smoking is causally associated with an increased risk of lower respiratory tract infections (pneumonia, bronchitis, and bronchiolitis). This report estimates that exposure to ETS contributes 150,000 to 300,000 lower respiratory tract infections annually in infants and children less than 18 months of age, resulting in 7,500 to 15,000 hospitalizations. These higher risks continue at a decreasing rate for children until about age 3, but no estimates are derived for children over 18 months.
3. a. Exposure to ETS is causally associated with additional episodes and increased severity of asthma in children who already have the disease. This report estimates that ETS exposure exacerbates symptoms in approximately 20% of this country's 2 million to 5 million asthmatic children and is a major aggravating factor in approximately 10%.

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b. In addition, the epidemiologic evidence is suggestive but not conclusive that ETS exposure increases the number of new cases of asthma in children who have not previously exhibited symptoms. Based on this evidence and the known ETS effects on both the immune system and lungs (e.g. atopy and airway hyperresponsiveness), this report concludes that ETS is a risk factor for the induction of asthma in previously asymptomatic children. Data suggest that relatively high levels of exposure are required to induce new cases of asthma in children. This report estimates that previously asymptomatic children exposed to ETS from mothers who smoke at least 10 cigarettes per day will exhibit a probable range of 8,000 to 26,000 new cases of asthma annually. The confidence in this range is medium and is dependent on the conclusion that ETS is a risk factor for asthma induction.

4. Passive smoking has subtle but significant effects on the respiratory health of nonsmoking adults, including coughing, phlegm, chest discomfort, and reduced lung function.

This report also has reviewed data on the relationship of maternal smoking and sudden infant death syndrome (SIDS), which is thought to involve some unknown respiratory pathogenesis. The report concludes that while there is strong evidence that infants whose mothers smoke are at an increased risk of dying from SIDS, available studies do not allow us to differentiate whether and to what extent this increase is related to in utero versus postnatal exposure to tobacco smoke products. Consequently, at this time this report is unable to assert whether or not ETS exposure by itself is a risk factor for SIDS independent of smoking during pregnancy. Postnatal exposure may potentiate effects of in utero tobacco smoke exposure, or it may not have any additional effect.

Regarding an association of parental smoking with either upper respiratory tract infections (colds and sore throats) or acute middle ear infections in children, this report finds the evidence inconclusive.

1.2.1. ETS and Lung Cancer

The Surgeon General (U.S. DHHS, 1989) estimated that smoking was responsible for more than one of every six deaths in the United States and that it accounted for about 90% of the lung cancer deaths in males and about 80% in females in 1985. Smokers, however, are not the only

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ones exposed to tobacco smoke. The sidestream smoke (SS) emitted from a smoldering cigarette between puffs (the main component of ETS) has been documented to contain many of the same carcinogenic compounds (known and suspected human and animal carcinogens) that have been identified in the mainstream smoke (MS) inhaled by smokers. Exposure concentrations of these carcinogens to passive smokers are variable but much lower than for active smokers. An excess cancer risk from passive smoking, however, is biologically plausible.

Based on the firmly established causal association of lung cancer with active smoking with a dose-response relationship down to low doses (Chapter 4), passive smoking is considered likely to affect the lung similarly. The widespread presence of ETS in both home and workplace and its absorption by nonsmokers in the general population have been well documented by air sampling and by body measurement of biomarkers such as nicotine and cotinine (Chapter 3). This raises the question of whether any direct evidence exists for the relationship between ETS exposure and lung cancer in the general population and what its implications may be for public health. This report addresses that question by reviewing and analyzing the evidence from 30 epidemiologic studies of effects from normally occurring environmental levels of ETS (Chapter 5). Because there is widespread exposure and it is difficult to construct a truly unexposed subgroup of the general population, these studies compare individuals with higher ETS exposure to those with lower exposures. Typically, female never-smokers who are married to a smoker are compared with female never-smokers who are married to a nonsmoker. Some studies also consider ETS exposure of other subjects (i.e., male never-smokers and long-term former smokers of either sex) and from other sources (e.g., workplace and home exposure during childhood), but these studies are fewer and represent fewer cases, and they are generally excluded from the analysis presented here. Use of the female never-smoker studies provides the largest, most homogeneous database for analysis to determine whether an ETS effect on lung cancer is present. This document assumes that the results for female never-smokers are generalizable to all nonsmokers.

Given that ETS exposures are at actual environmental levels and that the comparison groups are both exposed to appreciable background (i.e., nonspousal) ETS, any excess risk for lung cancer from exposure to spousal smoke would be expected to be small. Furthermore, the risk of lung cancer is relatively low in nonsmokers, and most studies have a small sample size, resulting in a very low statistical power (probability of detecting a real effect if it exists). Besides small sample size and low incremental exposures, other problems inherent in several of the studies may also limit their ability to detect a possible effect. Therefore, this document examines the data in several different ways. After downward adjustment of the relative risks for smoker

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misclassification bias, the studies are individually assessed for strength of association and exposure-response trend. Then the study results are pooled by country using statistical techniques for combining data, including both positive and nonpositive results, to increase the ability to determine whether or not there is an association between ETS and lung cancer. Finally, in addition to the previous statistical analyses that weigh the studies only by size, regardless of design and conduct, the studies are qualitatively evaluated for potential confounding, bias, and likely utility to provide information about any lung carcinogenicity of ETS. Based on these qualitative considerations, the studies are categorized into one of four tiers and then statistically analyzed successively by tier.

Results from all of the analyses described above strongly support a causal association between lung cancer and ETS exposure. The overall proportion of individual studies found to show an association between lung cancer and ETS exposure is unlikely to occur by chance ($p < 0.005$). Similarly, the proportion showing a statistically significant dose-response trend ($p < 10^{-9}$) is highly supportive of a causal association. Combined results by country showed statistically significant associations for Greece (2 studies), Hong Kong (4 studies), Japan (5 studies), and the United States (11 studies), and in that order of strength of relative risk. Pooled results of the four Western European studies (three countries) actually showed a slightly stronger association than that of the United States, but it was not statistically significant, probably due to the smaller sample size. The combined results of the Chinese studies do not show an association between ETS and lung cancer; however, two of the four Chinese studies were designed mainly to determine the lung cancer effects of high levels of other indoor air pollutants indigenous to those areas, which would obscure a smaller ETS effect. These two Chinese studies do, however, provide very strong evidence on the lung carcinogenicity of these other indoor air pollutants, which contain many of the same components as ETS. When results are combined only for the other two Chinese studies, they demonstrate a statistically significant association for ETS and lung cancer.

The relative risks for Greece and Japan of 2.00 and 1.44, respectively, are probably the best estimates, because both female smoking prevalence and nontobacco-related lung cancer risks, which tend to dilute the estimates of ETS effects, are low in these two countries. Also, for the time period for which ETS exposure was of interest, spousal smoking is considered to be a better surrogate for ETS exposure in these societies than in Western countries, where other sources of ETS exposure (work, public places, and other nonhome environments) are generally higher.

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Based on these analyses and following the U.S. EPA *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 1986a), EPA concludes that environmental tobacco smoke is a Group A (known human) carcinogen. This conclusion is based on a total weight-of-evidence, principally:

- Biological plausibility. ETS is taken up by the lungs, and components are distributed throughout the body. The presence of the same carcinogens in ETS and mainstream smoke, along with the established causal relationship between lung cancer and active smoking with the dose-response relationships exhibited down to low doses, make it reasonable to conclude that ETS is also a lung carcinogen.
- Supporting evidence from animal bioassays and genotoxicity experiments. The carcinogenicity of tobacco smoke has been established in lifetime inhalation studies in the hamster, intrapulmonary implantations in the rat, and skin painting in the mouse. There are no lifetime animal inhalation studies of ETS; however, the carcinogenicity of ETS condensates has been demonstrated in intrapulmonary implantations and skin painting experiments. Positive results of genotoxicity testing for both MS and ETS provide corroborative evidence for their carcinogenic potential.
- Consistency of response. All 4 of the cohort studies and 20 of the 26 case-control studies observed a higher risk of lung cancer among the female never-smokers classified as exposed to ETS. Of the 17 studies judged to be of higher utility based on study design, execution, and analysis (Appendices A and C), 15 observed higher risks, and 6 of these increases were statistically significant, despite most having low statistical power. Evaluation of the total study evidence from several perspectives leads to the conclusion that the observed association between ETS exposure and increased lung cancer occurrence is not attributable to chance.
- Broad-based evidence. These 26 case-control and 4 prospective studies provide data from 8 different countries, employ a wide variety of study designs and protocols, and are conducted by many different research teams. Results from all countries, with the possible exception of two areas of China where high levels of other indoor air lung carcinogens were present, show small to modest increases in lung cancer associated with spousal ETS exposure. No alternative explanatory variables for the observed association between ETS and lung cancer have been indicated that would be broadly applicable across studies.

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- Upward trend in dose-response. Both the largest of the cohort studies, the Japanese study of Hirayama--200 lung cancer cases, and the largest of the case-control studies, the U.S. study by Fontham and associates (1991)--420 lung cancer cases and two sets of controls, demonstrate a strong dose-related statistical association between passive smoking and lung cancer. This upward trend is well supported by the preponderance of epidemiology studies. Of the total of 17 studies in which data are classified by exposure level, 11 were statistically significant for the trend despite most having low statistical power.
- Detectable association at environmental exposure levels. Within the population of married women who are lifelong nonsmokers, the excess lung cancer risk from exposure to their smoking husbands' ETS is large enough to be observed. Carcinogenic responses are usually detectable only in high-exposure circumstances, such as occupational settings, or in experimental animals receiving very high doses. In addition, effects are harder to observe when there is substantial background exposure in the comparison groups, as is the case here.
- Effects remain after adjustment for potential bias. Current and ex-smokers may be misreported as never-smokers, thus inflating the apparent cancer risk for ETS exposure. The evidence remains statistically significant and conclusive, however, after adjustments for smoker misclassification. For the United States, the summary estimate of relative risk from nine case-control plus two cohort studies is 1.19 (90% confidence interval [C.I.] = 1.04-1.35) after adjustment for misclassification ($p < 0.05$). For Greece, 2.00 (1.42, 2.83), Hong Kong, 1.61 (1.25, 2.06) and Japan, 1.44 (1.13, 1.85), the estimated relative risks are higher than those of the United States and more highly significant after adjusting for the potential bias.
- Confounding cannot explain the association. The broad-based evidence for an association found by independent investigators across several countries, as well as the positive dose-response trends observed in most of the studies that analyzed for them, make any single confounder highly unlikely as an explanation for the results. In addition, this report examined potential confounding factors (history of lung disease, home heat sources, diet, occupation) and concluded that none of these factors could account for the observed association between lung cancer and ETS.

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The individual risk of lung cancer from exposure to ETS does not have to be very large to translate into a significant health hazard to the U.S. population because of the large number of smokers and the widespread presence of ETS. Current smokers comprise approximately 26% of the U.S. adult population and consume more than one-half trillion cigarettes annually (1.5 packs per day, on average), causing nearly universal exposure to at least some ETS. As a biomarker of tobacco smoke uptake, cotinine, a metabolite of the tobacco-specific compound nicotine, is detectable in the blood, saliva, and urine of persons recently exposed to tobacco smoke. Cotinine has typically been detected in 50% to 75% of reported nonsmokers tested (50% equates to 63 million U.S. nonsmokers of age 18 or above).

The best estimate of approximately 3,000 lung cancer deaths per year in U.S. nonsmokers age 35 and over attributable to ETS (Chapter 6) is based on data pooled from all 11 U.S. epidemiologic studies of never-smoking women married to smoking spouses. Use of U.S. studies should increase the confidence in these estimates. Some mathematical modeling is required to adjust for expected bias from misclassification of smoking status and to account for ETS exposure from sources other than spousal smoking. Assumptions are also needed to relate responses in female never-smokers to those in male never-smokers and ex-smokers of both sexes, and to estimate the proportion of the nonsmoking population exposed to various levels of ETS. Overall, however, the assumptions necessary for estimating risk add far less uncertainty than other EPA quantitative assessments. This is because for ETS the extrapolation is based on a large database of human studies, all at levels actually expected to be encountered by much of the U.S. population.

The components of the 3,000 lung cancer deaths figure include approximately 1,500 female never-smokers, 500 male never-smokers, and 1,000 former smokers of both sexes. More females are estimated to be affected because there are more female than male nonsmokers. These component estimates have varying degrees of confidence; the estimate of 1,500 deaths for female never-smokers has the highest confidence because of the extensive database. The estimate of 500 for male never-smokers is less certain because it is based on the female never-smoker response and is thought to be low because males are generally subject to higher background ETS exposures than females. Adjustment for this higher background exposure would lead to higher risk estimates. The estimate of 1,000 lung cancer deaths for former smokers of both sexes is considered to have the lowest confidence, and the assumptions included are thought to make this estimate low as well.

Workplace ETS levels are generally comparable to home ETS levels, and studies using body cotinine measures as biomarkers demonstrate that nonhome exposures to ETS are often greater

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than exposure from spousal smoking. Thus, this report presents an alternative breakdown of the estimated 3,000 ETS-attributable lung cancer deaths between spousal and nonhome exposures. By extension of the results from spousal smoking studies, coupled with biological measurements of exposure, more lung cancer deaths are estimated to be attributable to ETS from combined nonhome exposures - 2,200 of both sexes - than from spousal exposure - 800 of both sexes. This home-versus-other-sources partitioning depends on current exposure estimates that may or may not be applicable to the exposure period of interest. Thus, this breakdown contains this element of uncertainty in addition to those discussed above with respect to the previous breakdown.

Other estimates of annual U.S. nonsmoker lung cancer deaths attributable to ETS developed in this document give a range of 2,500 to 3,300. These other estimates use both mortality and cotinine exposure data from the largest and best-designed U.S. study (Fontham et al., 1991). Relatively small differences in cotinine ratios, as measures of exposure from spousal smoking, can result in substantial variability in population risk estimates. The range suggested above provides an estimation of the uncertainty in these estimates. Overall, however, considering the multitude, consistency, and quality of all these studies, the weight-of-evidence conclusion that ETS is a known human lung carcinogen, and the limited amount of extrapolation necessary, the confidence in the estimate of approximately 3,000 lung cancer deaths is medium to high.

1.2.2. ETS and Noncancer Respiratory Disorders

Exposure to ETS from parental smoking has been previously linked with increased respiratory disorders in children, particularly in infants. Several studies have confirmed the exposure and uptake of ETS in children by assaying saliva, serum, or urine for cotinine. These cotinine concentrations were highly correlated with smoking (especially by the mother) in the child's presence. Nine million to twelve million American children under 5 years of age, or one-half to two-thirds of all children in this age group, may be exposed to cigarette smoke in the home (American Academy of Pediatrics, 1986).

With regard to the noncancer respiratory effects of passive smoking, this report focuses on epidemiologic evidence appearing since the two major reports of 1986 (NRC and U.S. DHHS) that bears on the potential association of parental smoking with detrimental respiratory effects in their children. These effects include symptoms of respiratory irritation (cough, sputum, or wheeze); acute diseases of the lower respiratory tract (pneumonia, bronchitis, and bronchiolitis); acute middle ear infections and indications of chronic middle ear infections (predominantly middle ear effusion); reduced lung function (from forced expiratory volume and flow-rate measurements);

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incidence and prevalence of asthma and exacerbation of symptoms in asthmatics; and acute upper respiratory tract infections (colds and sore throats). The more than 50 recently published studies reviewed here essentially corroborate the previous conclusions of the NRC and Surgeon General regarding respiratory symptoms, respiratory illnesses, and pulmonary function, and they strengthen support for those conclusions by the additional weight-of-evidence (Chapter 7). For example, new data on middle ear effusion strengthen previous evidence to warrant the stronger conclusion in this report of a causal association with parental smoking. Furthermore, recent studies establish associations between parental smoking and increased incidence of childhood asthma. Additional research also supports the hypotheses that in utero exposure to mother's smoke and postnatal exposure to ETS alter lung function and structure, increase bronchial responsiveness, and enhance the process of allergic sensitization, changes that are known to predispose children to early respiratory illness. Early respiratory illness can lead to long-term pulmonary effects (reduced lung function and increased risk of chronic obstructive lung disease).

This document also summarizes the evidence for an association between parental smoking and SIDS, which was not addressed in the 1986 NRC or Surgeon General reports. SIDS is the most common cause of death in infants ages 1 month to 1 year. The cause (or causes) of SIDS is unknown; however, it is widely believed that some form of respiratory pathogenesis is generally involved. The current evidence strongly suggests that infants whose mothers smoke are at an increased risk of dying of SIDS, independent of other known risk factors for SIDS, including low birthweight and low gestational age, which are specifically associated with active smoking during pregnancy. However, available studies do not allow this report to conclude whether that increased risk is related to in utero versus postnatal exposure to tobacco smoke products, or to both.

The 1986 NRC and Surgeon General reports conclude that both the prevalence of respiratory symptoms of irritation and the incidence of lower respiratory tract infections are higher in children of smoking parents. In the 18 studies of respiratory symptoms subsequent to the 2 reports, increased symptoms (cough, phlegm, and wheezing) were observed in a range of ages from birth to midteens, particularly in infants and preschool children. In addition to the studies on symptoms of respiratory irritation, nine new studies have addressed the topic of parental smoking and acute lower respiratory tract illness in children, and eight have reported statistically significant associations. The cumulative evidence indicates strongly that parental smoking, especially the mother's, causes an increased incidence of respiratory illnesses from birth up to the first 18 months to 3 years of life, particularly for bronchitis, bronchiolitis, and

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pneumonia. Overall, the evidence confirms the previous conclusions of the NRC and Surgeon General.

Recent studies also solidify the evidence for the conclusion of a causal association between parental smoking and increased middle ear effusion in young children. Middle ear effusion is the most common reason for hospitalization of young children for an operation.

At the time of the Surgeon General's report on passive smoking (U.S. DHHS, 1986), data were sufficient only to conclude that maternal smoking may influence the severity of asthma in children. The recent studies reviewed here strengthen and confirm these exacerbation effects. In addition, the new evidence is conclusive that ETS exposure increases the number of episodes of asthma in children who already have the disease. It is also suggestive that ETS exposure increases the number of new cases of asthma in children who have not previously exhibited symptoms, although the results are statistically significant only with children whose mothers smoke 10 or more cigarettes per day. While the evidence for new cases of asthma itself is not conclusive of a causal association, the consistent strong associations of ETS with both increased frequency and severity of the asthmatic symptoms and the established ETS effects on both the immune system and airway hyperresponsiveness lead to the conclusion that ETS is a risk factor for induction of asthma in previously asymptomatic children.

Regarding the effects of passive smoking on lung function in children, the 1986 Surgeon General and NRC reports both conclude that children of parents who smoke have small decreases in tests of pulmonary output function of both the larger and smaller air passages when compared with the children of nonsmokers. As noted in the NRC report, if ETS exposure is the cause of the observed decrease in lung function, the effect could be due to the direct action of agents in ETS or an indirect consequence of increased occurrence of acute respiratory illness related to ETS.

Results from eight studies on ETS and lung function in children that have appeared since those reports add some additional confirmatory evidence suggesting a causal rather than an indirect relationship. For the population as a whole, the reductions are small relative to the interindividual variability of each lung function parameter. However, groups of particularly susceptible or heavily exposed subjects have shown larger decrements. The studies reviewed suggest that a continuum of exposures to tobacco products starting in fetal life may contribute to the decrements in lung function found in older children. Exposure to tobacco smoke products inhaled by the mother during pregnancy may contribute significantly to these changes, but there is strong evidence indicating that postnatal exposure to ETS is an important part of the causal pathway.

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With respect to lung function effects in adults exposed to ETS, the 1986 NRC and Surgeon General reports found the data at that time inconclusive, due to high interindividual variability and the existence of a large number of other risk factors, but compatible with subtle deficits in lung function. Recent studies confirm the association of passive smoking with small reductions in lung function. Furthermore, new evidence also has emerged suggesting a subtle association between exposure to ETS and increased respiratory symptoms in adults.

There is some evidence suggesting that the incidence of acute upper respiratory tract illnesses and acute middle ear infections may be more common in children exposed to ETS. However, several studies failed to find any effect. In addition, the possible role of confounding factors, the lack of studies showing clear dose-response relationships, and the absence of a plausible biological mechanism preclude more definitive conclusions.

In reviewing the available evidence indicating an association (or lack thereof) between ETS exposure and the different noncancer respiratory disorders analyzed in this report, the possible role of several potential confounding factors was considered. These include other indoor air pollutants; socioeconomic status; effect of parental symptoms; and characteristics of the exposed child, such as low birthweight or active smoking. No single or combined confounding factors can explain the observed respiratory effects of passive smoking in children.

For diseases for which ETS has been either causally associated (lower respiratory tract infections) or indicated as a risk factor (asthma cases in previously asymptomatic children), estimates of population attributable risk can be calculated. A population risk assessment (Chapter 8) provides a probable range of estimates that 8,000 to 26,000 cases of childhood asthma per year are attributable to ETS exposure from mothers who smoke 10 or more cigarettes per day. The confidence in this range of estimates is medium and is dependent on the suggestive evidence of the database. While the data show an effect only for children of these heavily smoking mothers, additional cases due to lesser ETS exposure are also a possibility. If the effect of this lesser exposure is considered, the range of estimates of new cases presented above increases to 13,000 to 60,000. Furthermore, this report estimates that the additional public health impact of ETS on asthmatic children includes over 200,000 children whose symptoms are significantly aggravated and as many as 1,000,000 children who are affected to some degree.

This report estimates that ETS exposure contributes 150,000 to 300,000 cases annually of lower respiratory tract illness in infants and children younger than 18 months of age and that 7,500 to 15,000 of these will require hospitalization. The strong evidence linking ETS exposure to increased incidence of bronchitis, bronchiolitis, and pneumonia in young children gives these

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estimates a high degree of confidence. There is also evidence suggesting a smaller ETS effect on children between ages 18 months and 3 years, but no additional estimates have been computed for this age group. Whether or not these illnesses result in death has not been addressed here.

In the United States, more than 5,000 infants die of SIDS annually. It is the major cause of death in infants between the ages of 1 month and 1 year and the linkage with maternal smoking is well established. The Surgeon General and World Health Organization estimate that more than 700 U.S. infant deaths per year from SIDS are attributable to maternal smoking (U.S. CDC, 1991a). However, this report concludes that at present there is not enough direct evidence supporting the contribution of ETS exposure to declare it a risk factor or to estimate its population impact on SIDS.

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2. INTRODUCTION

An estimated 434,000 deaths per year in the United States, or more than one of every six deaths, are directly attributable to tobacco use, in particular cigarette smoking (CDC, 1991a; figures for 1988). Approximately 112,000 of these smoking-related deaths are from lung cancer, accounting for an estimated 87% of U.S. lung cancer mortality (U.S. DHHS, 1989; percentage for 1985). Cigarette smoking is also causally related to cancer at various other sites, such as the bladder, renal pelvis, pancreas, and upper respiratory and digestive tracts (IARC, 1986). Roughly 30,000 deaths per year from cancers at these sites are attributable to smoking (CDC, 1991a). Furthermore, smoking is the major cause of chronic obstructive pulmonary disease (COPD), which includes emphysema, and is thought to be responsible for approximately 61,000 COPD deaths yearly, or about 82% of COPD deaths (U.S. DHHS, 1989). Tobacco use is also a major risk factor for cardiovascular diseases, the leading cause of death in the United States. It is estimated that each year 156,000 heart disease deaths and 26,000 deaths from stroke are attributable to smoking (CDC, 1991a). In addition to this substantial mortality, the association of smoking with these conditions also involves significant morbidity.

Smoking is also a risk factor for various respiratory infections, such as influenza, bronchitis, and pneumonia. An estimated 20,000 influenza and pneumonia deaths per year are attributable to smoking (CDC, 1991a). Smokers also suffer from lung function impairment and numerous other respiratory symptoms, such as cough, phlegm production, wheezing, and shortness of breath. In addition, smokers are at increased risk for a variety of other conditions, including pregnancy complications and ulcers.

Although the exact mechanisms and tobacco smoke components associated with these health effects are not known with certainty, more than 40 known or suspected human carcinogens have been identified in tobacco smoke. These include, for example, benzene, nickel, polonium-210, 2-napthylamine, 4-aminobiphenyl, formaldehyde, various N-nitrosamines, benz[a]anthracene, and benzo[a]pyrene. Many other toxic agents, such as carbon monoxide, nitrogen oxides, ammonia, and hydrogen cyanide, are also found in tobacco smoke.

Smokers, however, are not the only ones at risk from exposure to these tobacco smoke toxicants. In utero exposure from maternal smoking is known to be associated with low birthweight and increased risk of fetal and infant death (U.S. DHHS, 1989). Furthermore, nonsmokers might be at risk for smoking-associated health effects from passive exposure to environmental tobacco smoke (ETS). When a cigarette is smoked, approximately half of the

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smoke generated is sidestream smoke (SS) emitted from the smoldering cigarette between puffs. This SS constitutes roughly 85% of ETS (Fielding, 1985).

Twenty-eight percent of the U.S. adult population (CDC, 1991b), or about 50 million Americans, are smokers, and so virtually all Americans are exposed to some amount of ETS in the home, at work, or in public places. In view of the high levels of mortality and morbidity associated with smoking and the considerable potential for exposure of nonsmokers to ETS, passive smoking is potentially a substantial public health concern.

2.1. FINDINGS OF PREVIOUS REVIEWS

The first epidemiologic results associating passive smoking with lung cancer appeared in the early 1980's. Since then, two major comprehensive reviews of the health effects of passive smoking, and several less extensive ones have been published. One of the major reviews was conducted by the National Research Council (NRC) in 1986. At the request of two Federal agencies, the U.S. Environmental Protection Agency and the U.S. Department of Health and Human Services, the NRC formed a committee on passive smoking to evaluate the methods for assessing exposure to ETS and to review the literature on all of the potential health consequences of exposure. The committee's report (NRC, 1986) addresses the issue of lung cancer risk in considerable detail and includes summary analyses from 10 case-control studies and 3 cohort (prospective) studies. The report concludes that "[c]onsidering the evidence as a whole, exposure to ETS increases the incidence of lung cancer in nonsmokers." Combining the data from all the studies, the committee calculated an overall observed relative risk estimate of 1.34 (95% C.I. = 1.18-1.53).

The NRC committee was concerned about potential bias in the study results caused by current and former smokers incorrectly self-reported as lifelong nonsmokers (never-smokers). Using plausible assumptions for misreported smoking habits, the committee determined that smoker misclassification cannot account for all of the increased risk observed in the epidemiologic studies. Furthermore, the upward bias on the relative risk of lung cancer caused by smoker misclassification is counterbalanced by the downward bias from background ETS exposure to the supposedly unexposed group. Correcting for smoker misclassification and background ETS exposure, the committee calculated an overall adjusted relative risk estimate of 1.42 (range of 1.24 to 1.61) for lung cancer in nonsmokers from exposure to ETS from spousal smoking plus background sources.

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The NRC committee also found evidence for noncancer respiratory effects in children exposed to ETS. It recommended that "[i]n view of the weight of the scientific evidence that ETS exposure in children increases the frequency of pulmonary symptoms and respiratory infections, it is prudent to eliminate smoking and resultant ETS from the environments of small children." Furthermore, the committee concluded that "[h]ousehold exposure to ETS is linked with increased rates of chronic ear infections and middle ear effusions in young children." The NRC report also notes that "[e]vidence has accumulated indicating that nonsmoking pregnant women exposed to ETS on a daily basis for several hours are at increased risk for producing low-birthweight babies, through mechanisms which are, as yet, unknown."

The second major review, the Surgeon General's report on the health consequences of passive smoking, also appeared in 1986 (U.S. DHHS, 1986). This review covers ETS chemistry, exposure, and various health effects, primarily lung cancer and childhood respiratory disease. On the subject of lung cancer, the report concludes:

> The absence of a threshold for respiratory carcinogenesis in active smoking, the presence of the same carcinogens in mainstream and sidestream smoke, the demonstrated uptake of tobacco smoke constituents by involuntary smokers, and the demonstration of an increased lung cancer risk in some populations with exposures to ETS leads to the conclusion that involuntary smoking is a cause of lung cancer.

With respect to respiratory disorders in children, the Surgeon General's report determined that "[t]he children of parents who smoke, compared with the children of nonsmoking parents, have an increased frequency of respiratory infections, increased respiratory symptoms, and slightly smaller rates of increase in lung function as the lung matures."

In 1987, a committee of the International Agency for Research on Cancer (IARC) issued a report on methods of analysis and exposure measurement related to passive smoking (IARC, 1987). The committee reviewed the physicochemical properties of ETS, the toxicological basis for lung cancer, and methods of assessing and monitoring exposure to ETS. The report borrows the summary statement on passive smoking from a previous IARC document that dealt mainly with tobacco smoking (IARC, 1986). The working group that produced the 1986 report had found that the epidemiologic evidence then available on passive smoking was compatible with either the presence or the absence of a lung cancer risk; however, based on other considerations related to biological plausibility, it concluded that passive smoking gives rise to some risk of cancer. Specifically, the 1986 IARC report states:

> Knowledge of the nature of sidestream and mainstream smoke, of the materials absorbed during "passive smoking," and of the quantitative relationships between

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> dose and effect that are commonly observed from exposure to carcinogens . . . leads to the conclusion that passive smoking gives rise to some risk of lung cancer.

More recently, the Working Group on Passive Smoking, an independent international panel of scientists supported in part by RJR Reynolds Nabisco, reported the findings of its comprehensive "best evidence synthesis" of over 2,900 articles on the health effects of passive smoking (Spitzer et al., 1990). The group concluded that "[t]he weight of evidence is compatible with a positive association between residential exposure to environmental tobacco smoke (primarily from spousal smoking) and the risk of lung cancer." It also found "strong evidence that children exposed in the home to environmental tobacco smoke have higher rates of hospitalization (50 to 100%) for severe respiratory illness" and that the "evidence strongly supports a relationship between exposure to environmental tobacco smoke and asthma among children." In addition, the working group reported that there is evidence for associations between home ETS exposure and many chronic and acute respiratory illnesses, as well as small decreases in physiologic measures of respiratory function, in both children and adults. Evidence demonstrating an increased prevalence of otitis media (inflammation of the middle ear) in children exposed to ETS at home was also noted. With respect to in utero exposure, the group concluded that active maternal smoking is associated with reduced birthweight and with increased infant mortality.

A recent review of the health effects associated with adult workplace exposure to ETS conducted by the National Institute for Occupational Safety and Health (NIOSH, 1991) determined that "the collective weight of evidence (i.e., that from the Surgeon General's reports, the similarities in composition of MS [mainstream smoke] and ETS, and the recent epidemiologic studies) is sufficient to conclude that ETS poses an increased risk of lung cancer and possibly heart disease to occupationally exposed workers." Furthermore:

> Although these data were not gathered in an occupational setting, ETS meets the criteria of the Occupational Safety and Health Administration (OSHA) for classification as a potential occupational carcinogen [Title 29 of the Code of Federal Regulations, Part 1990]. NIOSH therefore recommends that exposures be reduced to the lowest feasible concentration.

The classification of "potential occupational carcinogen" is NIOSH's category of strongest evidence for carcinogenicity.

2.2. EPA's 1992 DOCUMENT

2.2.1. Scope

Due to the serious health concerns that have arisen regarding ETS, the most ubiquitous indoor air pollutant, and the wealth of new information that has become available since the

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extensive 1986 reviews, the EPA has performed its own analytical hazard identification and risk assessment for the respiratory health effects of passive smoking, based on a critical review of the data currently available, with an emphasis on the abundant epidemiologic evidence. The number of lung cancer studies analyzed in this document is more than double the number reviewed in 1986 (31 vs. 13), with a total of about 3,000 lung cancer cases in female nonsmokers now reported in case-control studies and almost 300,000 female nonsmokers followed by cohort studies. Furthermore, the database on passive smoking and respiratory disorders in children contains more than 50 new studies, including 8 additional studies on acute lower respiratory tract illnesses, 9 on acute and chronic middle ear diseases, 18 on respiratory symptoms, 9 on asthma, and 8 on lung function. This report also discusses six recent studies of the effects of passive smoking on adult respiratory symptoms and lung function. Finally, eight studies of maternal smoking and sudden infant death syndrome (SIDS), which was not addressed in the NRC report or the Surgeon General's report, are reviewed. (Although the cause of SIDS is unknown, the most widely accepted hypotheses suggest that some form of respiratory pathogenesis is usually involved.)

First, this document reviews information on the nature of ETS and human exposures. Then, in accordance with the *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 1986a), it critically analyzes human, animal, and genotoxicity data to establish the weight-of-evidence for the hazard identification of ETS as a human lung carcinogen and to characterize the U.S. population risk. Similarly, it reviews studies of passive smoking and noncancer respiratory disorders, particularly in children, and provides both hazard identification and population risk estimates for some of these effects.

While this report restricts analysis to ETS-associated respiratory effects because of time and resource considerations, several recent studies have also linked passive smoking with an increased risk of heart disease or cancers at sites other than the lung. For cancers of other sites, the available evidence is quite limited (e.g., Hirayama, 1984; Sandler et al., 1985), but three recent analyses, examining over 15 epidemiologic studies and various supporting mechanistic studies, suggest that ETS is an important risk factor for heart disease, accounting for as many as 35,000 to 40,000 deaths annually (Wells, 1988; Glantz and Parmley, 1991; Steenland, 1992). This report takes no position on ETS and heart disease.

Other health effects of active smoking may also have passive smoking correlates of public health concern. Maternal smoking during pregnancy, for example, is known to affect fetal development. Studies on passive smoking during pregnancy are far fewer but have demonstrated an apparent association with low birthweight (e.g., Martin and Bracken, 1986). Furthermore,

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passive exposure to tobacco smoke products both in utero and postnatally may result in other nonrespiratory developmental effects in children--for example, decrements in neurological development (Makin et al., 1991). Again, this document takes no position on these potential nonrespiratory effects.

2.2.2. Use of EPA's Guidelines

The lung cancer hazard identification and risk characterization for ETS are conducted in accordance with the EPA's *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 1986a). In fact, tobacco smoke is a mixture of over 4,000 compounds and could be evaluated according to the *Guidelines for the Health Risk Assessment of Chemical Mixtures* (U.S. EPA, 1986b). Such a highly complex mixture, however, is not easily characterized with respect to chemical composition, levels of exposure, and toxicity of constituents. Furthermore, the effects and mechanisms of interactions among chemicals are insufficiently understood.

The *Guidelines for the Health Risk Assessment of Chemical Mixtures* acknowledges these inherent uncertainties and recommends various assessment approaches, depending on the nature and quality of the data. When adequate data are available on health effects and exposure for the actual mixture of concern, as is the case with both MS and ETS, the preferred approach, according to the mixtures guidelines, is to adopt the procedures used for single compounds described by the *Guidelines for Carcinogen Risk Assessment*, as is done here. The EPA has also used this strategy for assessments of diesel exhausts, PCBs, and unleaded gasoline. The compilation of health effects and exposure information for all the mixture components of interest is considered optional. In the case of tobacco smoke, compiling this information would be highly impractical due to the large number of components and the highly complex and changing nature of this mixture. It is also considered unnecessary, given the abundant epidemiologic data on ETS and lung cancer.

The *Guidelines for Carcinogen Risk Assessment* provide a general framework for the analysis of carcinogenic risk, while permitting "sufficient flexibility to accommodate new knowledge and new assessment methods as they emerge" (U.S. EPA, 1986a). According to the guidelines, a qualitative risk assessment, or hazard identification, is performed by evaluating all of the relevant data to determine if a compound has carcinogenic potential. Then, a dose-response assessment is made by using mathematical models to extrapolate from high experimental or occupational exposures, where risks are usually detected, to lower environmental exposure levels.

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Finally, the dose-response assessment and an exposure assessment are integrated into a risk characterization, providing risk estimates for exposed populations.

The enormous database on active and passive smoking provides more than sufficient human evidence on which to base a hazard identification of ETS. The use of human evidence eliminates the uncertainty that normally arises when one has to base hazard identification on the results of high-dose animal experiments. Furthermore, the epidemiologic data on passive smoking provide direct evidence from environmental exposure levels, obviating the need for a dose-response extrapolation from high to low doses. These low-level environmental exposures, however, are associated with low relative risks that can only be detected in well-designed studies of sufficiently large size. For this reason, new assessment methods are used to categorize studies on the basis of quality criteria and to combine studies to increase the statistical power.

As an alternative to using actual epidemiologic data on ETS, an ETS risk assessment could have used "cigarette equivalents" to correlate ETS exposure with lung cancer risk based on dose-response models from active smoking. This would have involved using measures such as cotinine or respirable suspended particles to compare smoke uptake between smokers and ETS-exposed nonsmokers in order to equate passive smoking to the active smoking of some quantity of a cigarette(s). Then the carcinogenic response associated with that exposure level would be estimated from extrapolation models based on the dose-response relationships observed for active smoking. This procedure was not used for several reasons. Although MS and ETS are qualitatively similar with respect to chemical composition (i.e., they contain most, if not all, of the same toxicants and carcinogens), the absolute and proportional quantities of the components, as well as their physical state, can differ substantially. Many tobacco smoke compounds partition preferentially into the MS component of smoke emissions; others, however, such as certain highly carcinogenic N-nitrosamines, are preferentially produced at lower temperatures and appear in much greater amounts in the ETS fraction. In addition, active and passive smokers have different breathing patterns, and particles in ETS are smaller than those in MS. Therefore, the distribution and deposition of smoke constituents in the respiratory tracts of active and passive smokers will not be identical. Furthermore, it is not known which of the chemicals in tobacco smoke are responsible for its carcinogenicity. Clearly the comparison of a small number of biomarker measures cannot adequately quantify differential distributions of unknown carcinogenic compounds.

Another area of uncertainty in the "cigarette equivalents" approach relates to potential metabolic differences between active and passive smokers. Active smoking is known to induce

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chemical- and drug-metabolizing enzymes in various tissues to levels that significantly exceed those found in nonsmokers. Thus, the dose-response relationships for tobacco smoke-associated health effects are likely to be nonlinear. In fact, evidence suggests that a linear dose-response extrapolation might underestimate the risk of adverse health effects from low doses of tobacco smoke (Remmer, 1987). Because of these uncertainties, the data from active smoking are more appropriate for qualitative hazard identification than for quantitative dose-response assessment. Furthermore, at least for lung cancer and other respiratory effects, we have substantial epidemiologic data from actual exposure of nonsmokers to environmental levels of genuine ETS, which constitute a superior database from which to derive quantitative risk estimates for passive smoking, without the need for low-dose extrapolation.

2.2.3. Contents of This Document

ETS is chemically similar to MS, containing most, if not all, of the same toxicants and known or suspected human carcinogens. A major difference, however, is that ETS is rapidly diluted into the environment, and consequently, passive smokers are exposed to much lower concentrations of these agents than are active smokers. Therefore, in assessing potential health risks attributable to ETS, it is important to be able to measure ETS levels in the many environments where it is found and to quantify actual human ETS exposure. The physical and chemical nature of ETS and issues related to human exposure are discussed in Chapter 3. The use of marker compounds and various methods for assessing ambient ETS concentrations, as well as the use of biomarkers, questionnaires, and modeling techniques to determine human exposure, is described. Furthermore, measurements of ETS components in various indoor environments and of ETS constituents and their metabolites in adult and child nonsmokers are presented, providing evidence of actual nonsmoker exposure and uptake.

Chapter 4 reviews the major evidence that conclusively established that the tobacco smoke inhaled from active smoking is a human lung carcinogen. Unequivocal dose-response relationships exist between tobacco smoking and lung cancer, with no evidence of a threshold level of exposure. Supporting evidence for the carcinogenicity of tobacco smoke from animal bioassays and genotoxicity experiments is also summarized, including data from the limited animal and mutagenicity studies pertaining specifically to ETS.

The chemical similarity between MS and ETS and the measurable uptake of ETS constituents by nonsmokers (Chapter 3), as well as the causal dose-related association between tobacco smoking and lung cancer in humans, extending to the lowest observed doses, and the

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corroborative evidence for the carcinogenicity of both MS and ETS provided by animal bioassays and genotoxicity studies (Chapter 4), clearly establish the biological plausibility that ETS is also a human lung carcinogen. In fact, this evidence is sufficient in its own right to establish weight-of-evidence for ETS as a Group A (known human) carcinogen under EPA guidelines.

In addition to the evidence of human carcinogenicity from high exposures to tobacco smoke from active smoking, there are now more than 30 epidemiologic studies investigating lung cancer in nonsmokers exposed to actual ambient levels of ETS. The majority of these studies examine never-smoking women, with spousal smoking used as a surrogate for ETS exposure. Female exposure from spousal smoking is considered to be the single surrogate measure that is the most stable and best represents ETS exposure.

For the purposes of the hazard identification analysis in Chapter 5, which is based primarily on the epidemiologic studies of ETS, this document extensively and critically evaluates 31 epidemiologic studies from 8 different countries, including 11 studies from the United States (Appendix A). More than half of these studies have appeared since the NRC and Surgeon General's reviews were issued in 1986. Two U.S. studies are of particular interest. The recently published five-center study of Fontham et al. (1991) is a well-designed and conducted case-control study with 429 never-smoking female lung cancer cases and two separate sets of controls. This is the largest case-control study to date, and it has a high statistical power to detect the small increases in lung cancer risk that might be expected from ambient exposures. Another large U.S. case-control study was the recent study by Janerich et al. (1990), with 191 cases. Both of these studies were supported by the National Cancer Institute.

In evaluating epidemiologic studies, potential sources of bias and confounding must also be addressed. Smoker misclassification of current and former smokers as never-smokers is the one identified source of systematic upward bias to the relative risk estimates. Therefore, prior to the statistical analyses of the epidemiologic data that are conducted in Chapter 5, the relative risk estimates from each study are adjusted for smoker misclassification using the methodology of Appendix B. Other potential sources of bias and confounding are discussed extensively in the course of Chapter 5.

Chapter 5 quantitatively and qualitatively analyzes the epidemiologic data to determine the weight-of-evidence for the hazard identification of ETS. First the individual studies are statistically assessed using tests for effect (i.e., association between lung cancer and ETS) and tests for dose-response trend. Then various combining analyses are performed to examine and compare the epidemiologic results for separate countries. The studies are also categorized into four tiers

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according to the utility of the study in terms of its likely ability to detect a possible effect, based on specific criteria for evaluating the design and conduct as displayed in Appendix C and the critical reviews in Appendix A. These tiers are integrated one at a time into statistical analyses, as an alternative method for evaluating the epidemiologic data that also takes into account qualitative considerations. Chapter 5 concludes with an overall weight-of-evidence determination for lung cancer based on the analyses in Chapters 3, 4, and 5.

In Chapter 6, the relative risk estimates from 11 U.S. studies of passive smoking and lung cancer are adjusted upward to correct for the systematic downward bias caused by background exposure to ETS from sources other than spousal smoke. Using additional assumptions to extend the results from female never-smokers to male never-smokers and long-term former smokers of both sexes, the population risk for U.S. nonsmokers is characterized by estimating the annual number of lung cancer deaths that are attributable to exposure from all sources of ETS. Separate estimates are calculated for background (workplace and other nonhome exposures) and spousal (home) exposures, as well as for female and male never-smokers and former smokers. Chapter 6 also discusses the sources of uncertainty and sensitivity in the lung cancer estimates.

The final two chapters address passive smoking and noncancer respiratory disorders. Both the NRC and Surgeon General's reports concluded that children exposed to ETS from parental smoking are at greater risk for various respiratory illnesses and symptoms. This document confirms and extends those conclusions with analyses of more recent studies. New evidence for an association between ETS and middle ear effusion, and for a role of ETS in the cause as well as in the prevalence and severity of childhood asthma, is reviewed. In addition, the evidence for an association between maternal smoking and SIDS is examined.

Chapter 7 reviews and analyzes epidemiologic studies of passive smoking and noncancer respiratory disorders, mainly in children. Possible biological mechanisms, additional risk factors, and the potential long-term significance of early effects on lung function are discussed. Then, the evidence indicating relationships between childhood exposure to ETS and acute respiratory illnesses, middle ear disease, chronic respiratory symptoms, asthma, and lung function impairment, and between maternal smoking and SIDS, is evaluated.

Passive smoking as a risk factor for noncancer respiratory health effects in adults is also analyzed in Chapter 7. The NRC and Surgeon General's reports concluded that adults exposed to ETS may exhibit small deficits in lung function but noted that it is difficult to determine the extent to which ETS impairs respiration because so many other factors can similarly affect lung

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function. More recent evidence and new statistical techniques allow the demonstration of subtle effects of ETS on lung function and respiratory health in adults.

Chapter 8 discusses potential confounding factors and possible sources of bias in the ETS studies that might affect the conclusions of Chapter 7. Chapter 8 also describes methodological and data considerations that limit quantitative estimation of noncancer respiratory health effects attributable to ETS exposure. Finally, the chapter develops population impact assessments for ETS-attributable childhood asthma and for infant/toddler bronchitis and pneumonia. Acute respiratory illnesses are one of the leading causes of morbidity and mortality during infancy and early childhood, and an estimated 2 to 5 million children under age 18 are afflicted with asthma. Therefore, even small increases in individual risk for these illnesses can result in a substantial public health impact.

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3. ESTIMATION OF ENVIRONMENTAL TOBACCO SMOKE EXPOSURE

3.1. INTRODUCTION

This chapter considers some of the major issues relevant to assessing human exposure to environmental tobacco smoke (ETS). Current information on the nature of ETS, use of marker or proxy compounds for ETS, measured personal exposures to ETS proxies, measured concentrations of ETS proxy air contaminants in various indoor environments, use of ETS biomarkers, current models for assessing ETS proxy concentrations, and use of questionnaires for assessing exposure to ETS is summarized and discussed.

In the course of a typical day, an individual spends varying amounts of time in a variety of microenvironments (e.g., residences, industrial and nonindustrial workplaces, automobiles, public access buildings, outdoors). While in these microenvironments, individuals are exposed to a broad and complex spectrum of organic and inorganic chemicals in gaseous and particle forms, as well as a range of viable particles.

ETS is a major source of indoor air contaminants because of the large, though decreasing, number of smokers in the population and the quantity and quality of the contaminants emitted into the environment from tobacco combustion (NRC, 1981, 1986). Although no national surveys have been published, the ubiquitous nature of ETS in indoor environments indicates that some unintentional inhalation of ETS by nonsmokers is unavoidable. The combustion of tobacco results in the emission of a particularly complex array of air contaminants into indoor microenvironments. The nature of the resultant ETS contaminant mix and eventual human exposure is the product of the interaction of several interrelated factors associated with the source, transport, chemical transformation, dispersal, and removal, as well as human activities. Efforts to determine adverse health and nuisance effects of ETS must address the issue of exposure to a complex mixture that occurs in a number of microenvironments and must recognize that assessing ETS exposures is inherently complicated. Fully assessing ETS exposures would involve determining the time-weighted sum of exposures to each constituent in a multiplicity of microenvironments. Because this cannot be done, a simplified approach using biological or atmospheric markers, or questionnaires is generally used.

Accurate methods of assessing ETS exposures are needed for conducting epidemiologic studies, for calculating risks, and for developing effective control measures to reduce or eliminate risks. In epidemiologic studies of ETS, accurate exposure information is crucial to minimize the effects of misclassification and the influence of confounders and to improve the probability of

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revealing exposure-response associations. In risk assessment, exposure assessment provides basic information on the exposure-distribution curve (populations at a range of exposures) for ETS and essential information to calculate dose. ETS exposure assessment is essential in developing cost-effective mitigation efforts to reduce or minimize ETS-associated risks and then to monitor progress toward the targeted risk reduction.

Effective exposure assessment efforts require the identification of the health or nuisance effect under study, the specification (when possible) of the biological response time of the effect, and the ascertainment of the individual air contaminant, general group of air contaminants, or contaminant source thought to be associated with that effect. It is difficult to identify a single effect associated with a single air contaminant exposure and even more difficult to determine a dose-response relationship. The outcome variable under study is generally part of an effect complex related to other risk variables (e.g., health status, age, race, diet, personal habits, occupation) and a variety of air contaminants emitted from a number of potential sources. It is important to specify the duration, frequency, and magnitude of exposure to specific contaminants or categories of contaminants on a time scale corresponding to the health or comfort effect. Such a specification is necessary if an appropriate and adequate exposure assessment effort is to be undertaken. For example, studies of ETS-associated chronic effects (e.g., cancer) would ideally have ETS exposure measures integrated over periods of years, whereas studies of ETS-associated acute effects (e.g., odor, eye irritation) require exposure measures over a period of a few minutes. Specification of the biological response time under study is important in developing an ETS exposure assessment strategy.

Exposure to individual air contaminants, categories of air contaminants, or sources of air contaminants found outdoors and indoors can be assessed by direct and indirect methods. Direct methods include personal monitoring and use of biological markers, measured in the subject population. The indirect method employs models to estimate exposures. The modeling approach can employ the use of stationary monitoring and questionnaires. Stationary monitoring, with passive or active methods, is used to measure concentrations of air contaminants in different environments. These measured concentrations are then combined with time activity patterns (time budgets) to determine the average exposure of an individual as the sum of the concentrations in each environment weighed by the time spent in that environment. Monitoring of contaminants might also be supplemented with the monitoring of factors in the environment that impact the contaminant levels measured (e.g., meteorological variables, primary compounds, ventilation). Measurement of these factors in a carefully chosen set of conditions can lead to models that

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predict concentrations in the absence of measured concentrations and provide a means of assessing the impact of efforts to reduce or eliminate exposures. Questionnaires are used to determine time activity patterns of individuals, to provide a simple categorization of potential exposure, and to obtain information on the properties of the environment that have an impact on the measured levels (e.g., presence of sources, source use).

3.2. PHYSICAL AND CHEMICAL PROPERTIES

ETS comprises aged exhaled mainstream smoke (MS) from the smoker, diluted sidestream smoke (SS) emitted from the smoldering tobacco between puffs, contaminants emitted into the air during the puff, and contaminants that diffuse through the cigarette paper (NRC, 1986; U.S. DHHS, 1986; Guerin et al., 1992). SS is the principal contributor to ETS.

Chemical characterization of MS and SS air contaminant emissions from cigarettes, cigars, or pipes is derived from laboratory-based studies that have typically used standardized testing protocols (Brunnemann et al., 1976; Wynder and Hoffman, 1967; Dube et al., 1982). The data available are primarily for tobacco combustion in cigarettes. These protocols employ smoking machines, set puff volumes and frequencies, and standardize air contaminant collection protocols (e.g., small chambers, Cambridge filters, chamber airflow rates). Existing protocols reflect conditions representative of human smoking practices of more than 30 years ago and do not reflect current human smoking parameters (NRC, 1986; U.S. DHHS, 1986). MS and SS air contaminant emission rates determined in these studies can be affected by a number of factors, such as puff volume, air dilution rate, paper porosity, and moisture content of the tobacco. Variability in any of the factors can affect the nature and quantity of the emissions.

Results of laboratory evaluations have indicated substantial similarities and some differences between MS and SS emissions from cigarettes (NRC, 1986; U.S. DHHS, 1986). The air contaminants emitted in MS and SS are very similar in their chemical composition. Differences in SS and MS emissions are attributable to differences in the temperature of combustion of the tobacco, pH, and degree of dilution with air, which is accompanied by a corresponding rapid decrease in temperature. SS is generated at a lower temperature (600°C vs. 900°C) and at a higher pH (6.7-7.5 vs. 6.0-6.7) than is MS. SS is diluted rapidly with air. The size of SS particles is smaller than MS particles (SS particle size is 0.01-1.0 μm, whereas MS particle size is 0.1-1.0 μm). At the higher pH of SS, the proportion of unprotonated nicotine in the smoke increases, with SS nicotine predominantly in the vapor phase, while, in MS, nicotine is principally particle phase.

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More than 4,000 compounds have been identified in laboratory-based studies of tobacco smoke (Dube et al., 1982). Part of the data available from these studies is shown in Table 3-1. It is immediately obvious from Table 3-1 that SS and MS contain many of the same notable air contaminants, including several known or suspected human toxic and carcinogenic agents (e.g., carbon monoxide, ammonia, nicotine, tobacco-specific nitrosamines, benzo[a]pyrene, benzene, cadmium, nickel, aromatic amines). More than 20 carcinogens have been identified in ETS. Many of these toxic and carcinogenic compounds are emitted at levels higher in SS than in MS. For example, *N*-Nitrosodimethylamine, a potent animal carcinogen, is emitted in quantities 20 to 100 times higher in SS than in MS. A number of recent studies indicate that although filtering MS (filter cigarettes) will reduce the MS emissions for a number of compounds, it does not substantially reduce the emission rates for most SS constituents, particularly for known toxic and carcinogenic compounds (Adams et al., 1987; Guerin et al., 1987; Higgins, 1987).

The available data indicate that tobacco combustion will result in the emission of known toxic and carcinogenic contaminants into the environment, resulting in exposure to these contaminants by nonsmokers. It is important to note, however, that although the SS emissions are higher than MS emissions for many compounds, the dilution rate into the environment of SS is rapid, thus substantially lowering actual exposure concentrations of the contaminants. In cases where the SS emissions or exhaled MS emissions are in direct proximity to a nonsmoker (e.g., an infant held by a smoking mother or father), the nonsmoker's exposure to ETS contaminants will be high.

Few emission data have been collected under conditions more typical of actual smoking conditions (e.g., using smokers rather than smoking machines). It is not known how the MS and SS air contaminant emission data for specific compounds generated by the standardized testing protocols compare to data gathered under conditions more representative of actual smoking.

3.3. ASSESSING ETS EXPOSURE

3.3.1. Markers for Environmental Tobacco Smoke

Although ETS is a major source of indoor air contaminants, the actual contribution of ETS to indoor air is difficult to assess in the background of many contaminants contributed from a variety of other indoor and outdoor sources. Relatively few of the thousands of individual constituents of the ETS mix have been identified and characterized. In addition, little is known about the role of individual ETS constituents in eliciting the adverse health and nuisance effects observed. However, the issue is not how to fully characterize the exposure to each ETS-related

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contaminant, but rather how to obtain accurate quantitative measures of exposure to the entire ETS mixture. The measurement of all components in ETS is not feasible, practical, or even desirable because of limitations in knowledge of the mixture components related to the effects of interest as well as the feasibility and cost of sampling. It is necessary then to identify a marker (also referred to as a tracer, proxy, indicator, or surrogate) for ETS that, when measured, will accurately represent the frequency, duration, and magnitude of exposure to ETS. These markers can be chemicals measured in the air, biomarkers, models, or simple questionnaires.

There are important issues related to the measurement of a given marker compound to represent exposure to ETS. Ideally, an air contaminant marker for ETS should (1) vary with source strength, (2) be unique to the source, (3) be easily detected in air at low concentrations, (4) be similar in emission rates for a variety of tobacco products, (5) occur in a consistent ratio in air to other ETS components in the complex mix, and (6) be easily, accurately, and cost-effectively measured (Leaderer, 1990). The marker can be a specific compound (e.g., nicotine) or much less specific (e.g., respirable suspended particle mass). These criteria for selecting a suitable marker compound are the ideal criteria. In practice, no single contaminant or class of contaminants has been identified that would meet all the criteria. Selection of a suitable marker for ETS is reduced to satisfying as many of the criteria for judging a marker as is practical. In using a marker, it is important to state clearly the role of the marker and to note its limitations.

A number of marker or proxy compounds have been used to represent ETS concentrations in both field and chamber studies. Nicotine, carbon monoxide, 3-ethenylpyridine, nitrogen dioxide, pyridine, aldehydes, nitrous acid, acrolein, benzene, toluene, myosmine, and several other compounds have been used or suggested for use as markers or proxies for the vapor phase constituents of ETS (NRC, 1981, 1986; U.S. DHHS, 1986; Hammond et al., 1987; Eatough et al., 1986; Löfroth et al., 1989; Leaderer and Hammond, 1991). Tobacco-specific nitrosamines, particle phase nicotine and cotinine, solanesol, polonium-210, benzo[a]pyrene, potassium, chromium, and respirable suspended particle (RSP) mass (RSP mass $\leq$ 2.5 μm) are among the air contaminants used or suggested for use as markers for particle phase constituents of ETS (NRC, 1981, 1986; U.S. DHHS, 1986; Leaderer and Hammond, 1991; Benner et al., 1989; Hammond et al., 1988; Rickert, 1984). All the markers employed to date have some problems associated with their use. For example, carbon monoxide, nitrogen oxides, benzene, and RSP have many indoor and outdoor sources other than the combustion of tobacco, while other compounds, such as nitrosamines and benzo[a]pyrene, are sufficiently difficult to measure (e.g., concentrations in

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smoking environments are low and the cost of collection and analysis of samples is high) that their use is very limited.

At the present time, vapor phase nicotine and respirable suspended particulate matter are widely and most commonly used as markers of the presence and concentration of ETS for a variety of reasons associated with their ease of measurement, existing knowledge on the their emission rates from tobacco combustion, and their relationship to other ETS contaminants.

Vapor phase nicotine, the dominant form of nicotine in ETS (NRC, 1986; U.S. DHHS, 1986; Hammond et al., 1987; Eatough et al., 1986; Eudy et al., 1985), accounts for approximately 95% of the nicotine in ETS and is a good marker air contaminant for ETS. It is specific to tobacco combustion and emitted in large quantities in ETS (NRC, 1981, 1986; U.S. DHHS, 1986; Rickert et al., 1984; Eatough et al., 1990). Chamber measurements have shown that nicotine concentrations vary with source strength (Hammond et al., 1987; Hammond and Leaderer, 1987) and show little variability among brands of cigarettes despite variations in MS emissions (Leaderer and Hammond, 1991; Rickert et al., 1984). Field studies have shown that weekly nicotine concentrations are highly correlated with the number of cigarettes smoked (Leaderer and Hammond, 1991; Hammond et al., 1987; Mumford et al., 1989; Hammond et al., 1989). One large field study (Leaderer and Hammond, 1991) showed that weekly nicotine concentrations were strongly correlated with measured RSP levels as well as with reported number of cigarettes smoked. In this study, the slope of the regression line was 10.8, similar to the RSP/nicotine level seen in chamber studies. The RSP intercept was equal to background levels in homes without smoking. A comparable study by Miesner et al. (1989) of particulate matter and nicotine in workplaces found a similar ratio between RSP and nicotine. The utility of nicotine as an ETS marker is enhanced by the fact that recent advances in air sampling have resulted in the development of a variety of validated and inexpensive passive and active monitoring methods for measuring nicotine in indoor air environments and for personal monitoring (Hammond et al., 1987; Hammond and Leaderer, 1987; Marbury et al., 1990; Eatough et al., 1989a; Koutrakis et al., 1989; U.S. DHEW, 1977; Muramatsu et al., 1984; Oldaker and Conrad, 1987). In addition, measurements of nicotine and cotinine, a metabolite of nicotine, in blood, urine, and saliva are used extensively as biomarkers of exposure to ETS.

The combustion of tobacco results in substantial emissions of RSP. One small chamber study using a smoking machine found the average particle emission rate for 15 Canadian cigarettes to be 24.1 mg per cigarette with a range of 15.8 to 36.0 mg per cigarette (Rickert et al., 1984). A large chamber study using smokers reported an average particle emission rate of 17.1 mg for 12

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brands of American cigarettes (Leaderer and Hammond, 1991). This study noted that emission rates among brands are similar. Included in the RSP are a number of compounds of direct health concern--for example, many of the polycyclic aromatic hydrocarbons (NRC, 1986; U.S. DHHS, 1986; Table 3-1). There are a number of accepted methods to measure personal RSP exposures and concentrations in indoor environments (Ogden et al., 1989).

Studies of personal exposures to RSP and of RSP levels in indoor environments have shown elevated levels of RSP when any ETS exposure was reported (NRC, 1986; U.S. DHHS, 1986; Leaderer and Hammond, 1991; Repace and Lowrey, 1980; Ishizu, 1980). One study found a strong correlation between weekly residential RSP levels and reported number of cigarettes smoked (Leaderer and Hammond, 1991). At low smoking and high ventilation rates, however, it may be difficult to separate the ETS-associated RSP in a background of RSP from other indoor sources (e.g., kerosene heaters) or even from outdoor sources. Efforts to model ETS exposures for the purpose of assessing risks and the impact of various mitigation measures have often focused on predicting ETS-associated RSP concentrations (e.g., Leaderer, 1988; Repace and Lowrey, 1980).

3.3.2. Measured Exposures to ETS-Associated Nicotine and RSP

3.3.2.1. *Personal Monitors*

Personal monitoring allows for a direct integrated measure of an individual's exposure. Personal air monitoring employs samplers (worn by individuals) that record the integrated concentration of a contaminant that individuals are exposed to in the course of their normal activity for time periods of several hours to several days. The monitors can be active (employing pumps to collect and concentrate the air contaminant) or passive (working on the principle of diffusion). As with biomarkers, personal monitoring provides an integrated measure of exposure to air contaminants across a number of environments in which an individual spends time, but it does not provide direct information on concentrations of the air contaminant of interest in individual environments or on the level of exposure in each environment unless samples are taken in only one environment or are changed with each change of environment. Supplemental information (e.g., air monitoring of spaces, time-activity patterns) is needed to determine the contribution of each microenvironment to total exposure.

There are relatively few studies reported that have measured personal exposures to ETS-associated nicotine and RSP for nonsmoking individuals. The few reported studies for personal exposure to nicotine are summarized in Table 3-2. Personal exposures associated with specific indoor environments are presented. The indoor environments include the nonindustrial

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workplace, homes, restaurants, public buildings, and transportation-related indoor spaces. Table 3-2 also highlights the wide range of indoor environments in which ETS exposures take place and the wide range of personal exposures encountered in those environments. It is important to note, however, that there are relatively few observations available and that the observations for non-workplace nicotine exposures is dominated by the Japanese data (Muramatsu et al., 1984), which may not be representative of personal exposures in the United States. Because the data are limited, specific conclusions related to the contribution of different indoor environments to personal nicotine exposures associated with passive smoke cannot be drawn. The data do indicate, however, that a wide range of exposures to ETS occur in a variety of indoor environments where smoking is permitted. The data also indicate that the occupational and residential environments are important sources of exposure to ETS because of the levels encountered, which are comparable, and the length of time individuals spend in them.

Those studies of personal exposure to RSP for nonsmoking individuals that have attempted to stratify the collected data by ETS exposure are shown in Table 3-3. Three of the five studies represent exposures integrated over several microenvironments (e.g., residential, public buildings, occupational), while two studies report exposures for the workplace only. Individuals reporting exposure to ETS have substantially higher integrated exposures to RSP than do those reporting no exposure. Passive smoke exposure resulted in increases in personal RSP exposures beginning at 18 to 64 $\mu g/m^3$. It is difficult to assess the ETS contribution to personal RSP levels for each indoor environment for the 24-hour RSP personal exposures. The contribution of each of these indoor environments must be substantially higher than the 24-hour averages presented, because exposures presumably did not take place during sleeping hours or in all microenvironments. Table 3-3 demonstrates that the contribution of ETS-related RSP in the work environment to personal exposure is important and variable.

The most extensive study of personal exposures to RSP clearly demonstrates the impact on RSP levels from exposure to ETS (Spengler et al., 1985). In this study, outdoor, indoor, and personal 24-hour concentrations of RSP (particle diameter ≤ 3.5 μm) were obtained for a nonsmoking sample of 101 individuals. Of the 101, 28 persons reported some exposure to ETS in either the home or workplace, while 73 reported no ETS exposure. The cumulative frequency distributions of RSP for the ETS-exposed and non-ETS-exposed individuals and measured outdoor levels are shown in Figure 3-1. Those reporting ETS exposure had mean personal RSP levels 28 $\mu g/m^3$ higher than those reporting no ETS exposure (Table 3-3). A larger variation in RSP concentrations was also seen for those reporting ETS exposure.

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3.3.2.2. *Measurements Using Stationary Monitors*

Concentrations of nicotine, RSP, and other ETS constituents in an enclosed space can exhibit a pronounced spatial and temporal distribution. The concentration is the result of a complex interaction of several important variables, including (1) the generation rate of the contaminants from the tobacco, (2) location in the space that smoking occurs, (3) the rate of tobacco consumption, (4) the ventilation or infiltration rate, (5) the concentration of the contaminants in the ventilation or infiltration air, (6) air mixing in the space, (7) removal of contaminants by surfaces or chemical reactions, (8) reemission of contaminants by surfaces, and (9) the effectiveness of any air cleaners that may be present. The choice of location for obtaining an RSP or nicotine measurement, the timing of sample collection, and the duration of sampling should take into consideration the aforementioned factors.

In the past several years, numerous studies have been conducted in a variety of indoor environments to determine the impact of tobacco combustion on levels of nicotine and RSP. These studies have employed a variety of protocols that used a diversity of air sampling techniques (e.g., passive, active, continuous integrative), sampled over highly varying timeframes (from minutes to several days), and collected highly variable information on factors affecting the measured concentrations (e.g., number of cigarettes smoked, volume of building, ventilation rates). In an attempt to present an overall view of the contribution of ETS to indoor air quality, only the summary results of the measured concentrations of ETS-associated nicotine and RSP will be discussed here. Several reviews of the studies evaluating the impact of ETS on indoor RSP levels have been conducted over the past few years, and a number of recent reports have discussed measured indoor levels of nicotine (e.g., NRC, 1986; U.S. DHHS, 1986; Leaderer and Hammond, 1991). More detailed information is provided in those reports and the individual study reports.

A summary of measured nicotine concentrations in various indoor environments where smoking was noted is summarized in Figure 3-2. The mean concentration, standard deviation, and maximum and minimum nicotine values recorded are presented. Also given in Figure 3-2 is the number of locations in which the measurements were taken and the reference in which the data were reported. Elevated nicotine levels were measured in all microenvironments in which smoking was reported. Measured nicotine levels, as would be expected, were highly variable, covering several orders of magnitude.

The home and workplace environments may represent the most important environments for exposure to ETS because of the length of time individuals spend there. For the four studies reported, nicotine levels in homes where smoking occurs ranged from less than 1 $\mu g/m^3$ (Leaderer

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and Hammond, 1991) to more than 14 $\mu g/m^3$ (U.S. DHEW, 1977). For two of the studies (Leaderer and Hammond, 1991; U.S. DHEW, 1977), nicotine concentrations represent weekly averages. Actual concentrations in the homes during nonsleeping occupancy (i.e., while smoking would be occurring) would be considerably higher than the levels presented in Figure 3-2 (a factor of 3 or higher). Workplace nicotine also demonstrated a wide range of concentrations, from near zero to more than 33 $\mu g/m^3$. In other environments, nicotine concentrations demonstrated considerable variability. It is important to note that short-term concentrations (on the order of minutes) are likely to show considerably more variability, resulting in considerably higher short-term peak exposures.

In one large study of residential levels of ETS-associated nicotine and RSP (Leaderer and Hammond, 1991), both were found to be highly correlated with reported number of cigarettes smoked. This study found that, consistent with chamber data, measured nicotine concentrations predicted the contribution to residential RSP levels from tobacco combustion (Figure 3-3). The data in Figure 3-3 might be used to estimate the RSP levels associated with tobacco combustion from the nicotine levels shown in Figure 3-2.

A substantial number of studies examining the impact of tobacco combustion on concentrations of RSP in various indoor environments have been reported. Many of these studies have reported outdoor RSP concentrations and indoor RSP levels without smoking as well as concentrations when smoking occurs. These studies are summarized in Figure 3-4. The sampling time for the presented data ranged from 1 minute to more than several days. A major portion of the data is for the residential indoor environment. Where smoking is reported, RSP levels are considerably higher than where it is not. RSP levels associated with smoking, like those for nicotine, demonstrated considerable variability ranging from a few $\mu g/m^3$ to more than 1 mg/m^3. Workplace RSP levels associated with smoking occupancy are comparable to residential RSP levels.

Indoor levels of nicotine and RSP associated with the combustion of tobacco are a function of several factors related to the generation, dispersal, and removal of ETS in enclosed environments. Thus, measured levels of these air contaminants indicate a wide range of concentrations. Figures 3-5 and 3-6 present a summary of the range of nicotine and ETS-associated particle concentrations measured by type of environment. The figures present the range of average values reported for each study and the minimum and maximum values reported. Only studies reporting sampling times over 4 hours were included in the residential and office summaries in Figures 3-5 and 3-6 because averaging time is more likely to represent the exposures associated with occupancy time (this included most of the studies for residential spaces shown in

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Figures 3-2 and 3-4). Because occupancy time in other environments (e.g., restaurants) is likely to be much shorter (for patrons, but not for service personnel), averaging times on the order of minutes or greater were considered for the other indoor environments presented in the figures. Indoor particulate levels associated with smoking occupancy (Figure 3-6) were calculated by subtracting particle levels for nonsmoking occupancy (presented in the studies) from the smoking occupancy levels. Thus, the increase in particle mass concentrations associated with ETS is presented in Figure 3-6.

The summary nicotine data (Figure 3-5) suggest that average nicotine values in residences with smoking occupancy will range from 2 $\mu g/m^3$ to approximately 10 $\mu g/m^3$, with high values up to 14 $\mu g/m^3$ and low values down to 0.1 $\mu g/m^3$. Average nicotine concentrations in offices with smoking occupancy show a range of average concentrations similar to that of residences, but with considerably higher maximum values. The data from other indoor spaces suggest considerable variability, particularly in the range of maximum values. The cumulative distribution of weekly nicotine measured in one study (Leaderer and Hammond, 1991) of a sample of 96 homes, with the levels for smoking occupancy emphasized, is shown in Figure 3-7.

Residential particle mass concentrations will increase from 18 to 95 $\mu g/m^3$ with smoking occupancy, while the recorded increases can be as high as 560 $\mu g/m^3$ or as low as 5 $\mu g/m^3$ (Figure 3-6). Figure 3-8 (Leaderer and Hammond, 1991) highlights the distribution of weekly RSP concentrations for residences with smoking occupancy. In that study, smoking residences had RSP concentrations approximately 29 $\mu g/m^3$ higher than nonsmoking homes. Average concentrations in offices with smoking occupancy will be lower on average than in residences. Restaurants, transportation, and other indoor spaces with smoking occupancy will result in a considerably wider range of average, minimum, and maximum increases in particle concentrations than in the residential or office environments.

As noted earlier, indoor air contaminant concentrations are the result of the interaction of a number of factors related to the generation, dispersal, and elimination of the contaminants. Source use is no doubt the most important factor. Few studies have measured contaminant concentrations as a function of the smoking rate in residences or offices, but some data are available. One study estimated an average weekly contribution to residential RSP of 2 to 5 $\mu g/m^3$ per cigarette (Leaderer et al., 1990), while another study estimated that a pack-a-day smoker would add 20 $\mu g/m^3$ to residential levels (Coghlin et al., 1989). Variations in residential RSP levels as a function of the number of smokers and over a period of several months are demonstrated in Figure 3-9 (Spengler et al., 1981). An association between the reported number

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of cigarettes and weekly residential nicotine and RSP levels for a sample of 96 homes (Leaderer and Hammond, 1991) is shown in Figure 3-10. Smoking clearly increases indoor concentrations of both nicotine and particle mass. Residential levels of both nicotine and particle mass increase with increasing levels of smoking. Because nicotine and particle mass are proxies for the complex ETS contaminant mix, it is expected that other ETS air contaminants, including the toxic and carcinogenic contaminants, will be elevated with smoking occupancy.

Children have been identified as a particularly sensitive group at health risk from exposure to ETS in the residential indoor environment (NRC, 1986; U.S. DHHS, 1986). One study has measured smoking status of the parents and weekly nicotine concentrations in the activity room and bedroom of 48 children under the age of 2 years. The results, shown in Table 3-4, indicate that activity room and bedroom concentrations of nicotine in the children's homes increase with the reported number of cigarettes smoked in the home by parents. Concentrations also increased with the number of reported smokers in the household. Correlation coefficients of more than 0.7 were calculated between nicotine concentrations and number of cigarettes smoked.

It is important to note that while measurements of nicotine and ETS-associated RSP are excellent indicators of the contribution of ETS to air contaminant levels in indoor environments, their measurement does not directly constitute a measure of total exposure. The concentrations measured in all indoor environments have to be combined with time-activity patterns in order to determine average exposure of an individual as the sum of the concentrations in each environment weighted by the time spent in that environment. Both the home and the work environment (those without policies restricting smoking) have highly variable ETS concentrations, the ranges of which are largely overlapping. Which environment is most important in determining total exposure will vary with individual circumstances. For example, one who lives in a smoker-free home but works in an office with smokers will receive most ETS exposure at work; however, for those exposed both at home and at work, the home may be more important because, over the course of a week, more time is spent at home (assuming equal exposure concentrations).

An additional issue to be considered is how well the general indoor concentrations represent exposures of individuals who may be directly exposed to the SS plume of ETS. Small children, particularly infants, being held by smoking parents may receive exposures considerably higher than those predicted from concentrations reported for indoor spaces. Special consideration must be given to these significant subpopulations.

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3.3.3. Biomarkers of ETS Exposure

Biomarkers of exposure are actually a measure of dose or uptake and hence an indicator that an exposure has taken place. Biomarkers, within the context of assessing exposure to air contaminants, refer to cellular, biochemical, or molecular measures that are obtained from biological media such as human tissues, cells, or fluids and are indicative of human exposure to air contaminants (Collier et al., 1990; Goldstein et al., 1987). The relation between the biomarker and exposure, however, is complex and varies as a function of several factors, including environmental factors and the uptake, distribution, metabolism, and site and mode of action of the compound or compounds of interest.

Ideally, a biomarker of exposure for a specific air contaminant should be chemically specific, have a long half-life in the body, be detectable in trace quantities with high precision, be measurable in samples easily collected by noninvasive techniques, be inexpensive to assay, be either the agent that is associated with the effects or strongly associated with the agent of interest, and be quantitatively relatable to a previous exposure regimen. Ideal biomarkers for air contaminants, such as markers for complex mixtures, do not exist.

Numerous biomarkers have been proposed as indicators for ETS (e.g., thiocyanate, carboxyhemoglobin, nicotine and cotinine, N-Nitrosoproline, aromatic amines, protein or DNA adducts) (NRC, 1986; U.S. DHHS, 1986). Although these biomarkers demonstrate that an exposure has taken place, they may not be directly related to potential for development of the adverse effect under study (not the contaminant directly implicated in the effect of interest), they can show considerable variability from individual to individual, and they represent only fairly recent exposure (potentially inadequate for chronic outcomes). Furthermore, some of these markers may not be specific to ETS exposure (e.g., carboxyhemoglobin), while others (e.g., thiocyanate) may not be sensitive enough for ETS exposures.

Nicotine and its metabolite, cotinine, in the saliva, blood, and urine are widely used as biomarkers of active smoking and exposure to ETS and are valuable in determining total or integrated short-term dose to ETS across all environments (NRC, 1986; U.S. DHHS, 1986). Nicotine and cotinine are specific to tobacco and are accurately measured by gas chromatography, radioimmunoassay, or high-pressure liquid chromatography in concentrations down to 1 ng/ml. Nicotine has a half-life typically of about 2 hours in the blood and is metabolized to cotinine and excreted in the urine. The short half-life of nicotine makes it a better indicator of very recent exposures rather than a measure of integrated exposure.

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Cotinine in saliva, blood, and urine is the most widely accepted biomarker for integrated exposure to MS or ETS (NRC, 1986; U.S. DHHS, 1986). Cotinine is the major metabolite of nicotine, is specific to tobacco, and has a longer half-life for elimination from the body. The elimination half-life in smokers is approximately 20 hours (range of 10 to 37 hours), while it is typically longer in nonsmokers with ETS exposure, particularly in children (Figure 3-11) (Elliot and Rowe, 1975; Collier et al., 1990; Goldstein et al., 1987; Etzel et al., 1985; Greenberg et al., 1984). The longer half-life of cotinine makes it a good indicator of integrated ETS exposure over the previous day or two. Laboratory studies of nonsmokers exposed to acute high levels of ETS over varying times have shown significant uptake of nicotine by the nonsmokers and increases in their cotinine levels (NRC, 1986; U.S. DHHS, 1986; Hoffmann et al., 1984; Russell and Feyerabend, 1975).

Several studies have been conducted of cotinine levels in free-living populations of smokers, nonsmokers reporting passive smoke exposure, and nonsmokers reporting no passive smoke exposure (NRC, 1986; U.S. DHHS, 1986; Greenberg et al., 1984; Wald et al., 1984; Wald and Ritchie, 1984; Jarvis, et al., 1985; Coultas et al., 1987; Riboli et al., 1990; Cummings et al., 1990). These studies have found that exposure to ETS is highly prevalent even among those living with a nonsmoker (e.g., Cummings et al., 1990). Saliva, serum, and urine cotinine levels in ETS-exposed nonsmokers were generally found to be higher than those in nonsmokers reporting no ETS exposure, and levels of cotinine in smokers are considerably higher than those levels in nonsmokers passively exposed (Table 3-5). Cotinine levels in nonsmokers exposed to ETS are on the order of approximately 1% of the levels in active smokers. Cotinine levels of nonsmokers have been found to increase with self-reported ETS exposure (Figures 3-12 and 3-13).

In a 10-country study of ETS exposure of 1,369 nonsmoking women (Riboli et al., 1990), average urinary levels of cotinine/creatinine by country ranged from approximately 2.5 ng/mg for Shanghai to approximately 14 ng/mg for Trieste. Eighty percent of those women sampled had a detectable level of cotinine. Statistically significant differences were observed between centers, with the lowest values observed in Honolulu, Shanghai, and Chandigarh and the highest values in Trieste, Los Angeles, and Athens. This study also found a linear increase in cotinine/creatinine levels for the group of women reporting no ETS exposure either at home or work to the group reporting ETS exposure both at home and at work (Figure 3-14). Urinary cotinine levels were also found to increase with the number of questionnaire-reported passive smoke exposures in a group of 663 persons who never smoked and ex-smokers (Cummings et al., 1990). In that study, 76% of the subjects reported passive smoke exposure, with 27% reporting exposure at home and

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28% reporting exposure at work. Jarvis et al. (1983) studied the increase of cotinine in 7 nonsmokers after 2 hours' exposure to ETS in a "smoky public house." They found highly statistically significant increases of cotinine in all body fluids: from 1.1 to 7.3 ng/mL in plasma, from 1.5 to 8.0 ng/mL in saliva, and from 4.8 to 12.9 ng/mL in urine. Because the samples were taken immediately post-exposure, they do not indicate peak cotinine concentrations, however.

Cotinine values in smokers and nonsmokers measured in either the laboratory or field setting show considerable variability attributable to individual differences in the uptake distribution, metabolism, and elimination of nicotine. An additional issue that has to be considered in interpreting the field data is that exposure status is determined by respondent self-reporting. This can lead to a misclassification error, which tends to reduce the differences in cotinine levels measured in the ETS-exposed versus non-ETS-exposed groups and to increase the variability in the levels within any exposure category. Within the exposed group, this misclassification error could either increase or decrease the average cotinine levels measured.

It is important to recognize that nicotine and cotinine are actually proxy biomarkers. They may not be the active agents in eliciting the adverse effect under study but merely indicative of the level of passive smoke exposure. Using these measures to estimate cigarette equivalents or to determine equivalent active smoking exposure could result in over- or underestimating exposure to individual or classes of compounds that may be more directly related to the health or nuisance effect of concern. The use of different biomarker proxies (e.g., protein adducts) could result in estimates of much larger cigarette equivalent doses.

Nicotine and cotinine levels in ETS-exposed nonsmokers measured in laboratory and field studies have been used to estimate cigarette equivalent exposures and to equate ETS exposures with active smoker exposures (NRC, 1986; U.S. DHHS, 1986; Jarvis, 1989). On an equivalent cigarette basis, an upper-bound estimate of nicotine dose of 2.5 mg per day for passive smoke exposure has been proposed (Jarvis, 1989). This would translate into the equivalent of about one-fifth of a cigarette per day, or about 0.7% of the average smoker's dose of nicotine (cigarette equivalent dose of other toxins or carcinogens would be different, as described above). Comparisons of cotinine values in ETS-exposed nonsmokers with those measured in smokers ranged from 0.1% to 2%. One analysis proposed that, on average, nonsmokers' cotinine levels are 0.5% to 0.7% of those found in cigarette smokers (Jarvis, 1989). It should be noted that these estimations are based on a number of assumptions that may not hold (e.g., the half-life of nicotine and cotinine in smokers and nonsmokers is the same).

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One of the protein adducts that has been used as a biomarker of active and passive smoking is the 4-aminobiphenyl adduct of hemoglobin (4-ABP-Hb). One advantage of hemoglobin adducts is that their half-life is quite long, and they will persist through the life of a red blood cell, which is approximately 120 days. Therefore, levels of 4-ABP-Hb reflect exposures over the past several weeks, rather than the day or two of exposure-integration reflected by cotinine measurements.

Tobacco smoke is the primary environmental source of 4-aminobiphenyl (its use in the dye industry was discontinued decades ago), and smokers have between five and eight times as much 4-ABP-Hb adducts as nonsmokers (Hammond et al., 1990; Perera et al., 1987; Maclure et al., 1989). That nonsmokers appear to have approximately 10% to 20% the adduct level as smokers may at first appear to be contradictory to the urinary cotinine ratios of about 1%, but in fact both results are quite consistent with our knowledge of the emissions of various contaminants in MS and SS. Approximately twice as much nicotine is emitted in SS as in MS, but about 31 times as much 4-ABP is emitted in SS as in MS. Thus, compared to MS, SS is 15 times more enriched in 4-ABP than in nicotine. The ratio of biomarkers in those exposed to ETS compared to smokers is 15 times greater for the biomarker 4-ABP-Hb than for the biomarker cotinine, a metabolite of nicotine.

The above discussions indicate that the "cigarette equivalent" dose of those exposed to ETS varies with the compound, so that a passive smoker may receive 1% as much nicotine as an active smoker but 15% as much 4-ABP. These commentaries on the data are preliminary and warrant further investigation, but they do suggest the importance of careful interpretation of biomarkers in estimating dose.

3.3.4. Questionnaires for Assessing ETS Exposures

Questionnaires are the most commonly used method to assess exposure to ETS in both retrospective studies of acute and chronic effects and in prospective studies. They are the least expensive method of obtaining ETS exposure information for large populations. They can be used to provide a simple categorization of ETS exposure, to determine time-activity patterns of individuals (e.g., how much time is spent in environments where smoking occurs), and to acquire information on the factors or properties of the environment affecting ETS concentrations (e.g., number of cigarettes smoked, size of indoor environments, subjective evaluation of level of smokiness). The time-activity pattern information is combined with measured or estimated concentrations of ETS in each environment to provide an estimate of total exposure. Information

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on the factors affecting ETS concentrations is used to model or predict ETS levels in those environments.

Questionnaires are used most extensively to provide a simple categorization of potential ETS exposure (e.g., Do you live with a smoker? Are you exposed to ETS at your place of work? How many hours a week are you exposed to ETS?) and to obtain information on possible confounders (e.g., occupational history, socioeconomic status). When used simply to determine a dichotomous exposure (ETS exposed vs. unexposed), any misclassification tends to bias measures of association toward the null. Thus, any effect that may be present will be underestimated or may even be undetectable. If there are more than two exposure categories (e.g., light, medium, or heavy exposure), the intermediate categories of exposure may be biased either away from or toward the null. Misclassification errors may arise from respondents' lack of knowledge, biased recall, memory failure, or intentional alteration of information. In addition, there are investigator-based sources of misclassification. Errors may arise if semiquantitative levels are incorrectly imputed to answers; for example, even if house exposures are higher than occupational exposures, on average, for any given individual, the ranking may well be reversed from that of the average.

In using questionnaires to assess exposure categories to ETS to determine time-activity patterns and to acquire information on the factors affecting concentrations, it is important to minimize the uncertainty associated with the estimate and to characterize the direction and magnitude of the error.

Unlike those for active smoking, standardized questionnaires for assessing ETS exposures in prospective or retrospective studies of acute or chronic health or nuisance effects do not exist. Questionnaires used to assess ETS exposure have typically not been validated. There is no "gold standard" with which to validate the questionnaire. Various strategies, however, have been used to assess the validity of diverse types of questionnaires used to assess ETS exposure. Efforts to validate questionnaires have used survey data, air monitoring of nicotine in various microenvironments, and nicotine or cotinine in body fluid samples.

One report (NRC, 1986) estimated an error rate of 5% in using surrogate responses in the simple classification of an individual as ever/never smoked. Such a classification scheme (e.g., married to a smoker) has been used to assess a nonsmoking spouse's exposure in the home for ETS-associated cancer outcome. A recent study (Leaderer and Hammond, 1991) of 96 homes using a questionnaire to assess residential smoking and a passive nicotine air monitor found that 13% of the residences reporting no smoking had measurable levels of nicotine, while 28% of the

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residences reporting smoking had nondetectable levels of nicotine. A good level of agreement between questionnaire-reported number of cigarettes smoked and residential levels of ETS-related RSP and nicotine was observed in this study (Figure 3-10).

Studies (Hammond et al., 1989; Schenker et al., 1990; Coultas et al., 1987; Riboli et al., 1990; Cummings et al. 1990; Coultas et al., 1990a) comparing various measures of ETS exposure (e.g., location of exposure, intensity of exposure, duration of exposure, number of cigarettes smoked) with cotinine levels measured in physiological fluids generally meet with only moderate success (explained variations on the order of 40% or less). The largest such study (Riboli et al., 1990) was a collaborative effort conducted in 10 countries; correlations in the range of 0.3 to 0.51 ($p < 0.01$) were found between urinary cotinine levels and various measures of exposure derived from questionnaire data. Using cotinine as a biomarker of exposure, studies indicated that a substantial percentage of those persons reporting no ETS exposure by questionnaire do have measurable exposure. Differences in the uptake metabolism and excretion of nicotine among individuals make it difficult to use this measure as a "gold standard" in validating questionnaires. Also, the recent exposure lasting 1 to 2 days that is measured by cotinine may differ from usual exposure.

In one effort to develop a validated questionnaire (Schenker et al., 1990), 53 subjects were asked detailed questions about their exposures to ETS, including location of exposures, number of smokers, ventilation characteristics, number of hours exposed, proximity of smokers, and intensity of ETS. They then wore a passive sampler for nicotine for 7 days and recorded the same information regarding each exposure episode in daily diaries. Formulae were developed to score the exposures on both the questionnaire and the diary, and these scores were then correlated to the average nicotine concentrations measured over the 7-day period. Excellent correlation was found ($r^2 = 0.83$ for the questionnaire and 0.90 for the diary). However, the simple questions that have most frequently been used in epidemiologic studies (e.g., whether a subject lived with a smoker, number of hours the subject was exposed) were not nearly as well correlated with the measured exposures. These results indicate that reliable questionnaires can be developed but that those used in most studies in the past will lead to some random misclassification of exposure and, hence, underestimation of any effect that may be present.

ETS exposures take place across a number of environments, with an individual's total exposure a function of the amount of time spent in each environment and the concentration in that environment. Questionnaires need to assess exposures across indoor environments. Personal air monitoring or the measurement of a biomarker provides a method to validate ETS exposure

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assessment questionnaires and to assess the contribution of each environment to total current exposure.

Personal air monitoring and cotinine measurements in combination with questionnaires have highlighted the importance of obtaining information on spouses' smoking status, smoking at home, smoking at work, smoking in various other indoor environments (e.g., social settings, vehicles, public places) amount of time in environments where smoking occurs, and the intensity of the exposure (Hammond et al., 1989; Schenker et al., 1990; Coultas et al., 1987; Riboli et al., 1990; Cummings et al. 1990; Coultas et al., 1990a).

3.4. MODELS FOR ASSESSING ETS EXPOSURE

Epidemiologic studies of ETS ideally should have direct measurements of the ETS exposures for the target individuals or populations. It is, however, neither practical nor possible in most instances to obtain such measurements. For example, in retrospective studies of lung cancer or respiratory illnesses, air samples of contaminant levels in various microenvironments or personal air sampling cannot be obtained. Current measurements may not be directly relevant because exposures have changed over the past 20 years. In such cases, past and present ETS exposures can be modeled. Models that predict ETS concentrations in various microenvironments can be used either to estimate total exposure in combination with time-activity patterns or to estimate the impact of variations in factors (e.g., number of cigarettes smoked, changes in ventilation rates) that have an impact on microenvironmental concentrations. Models used for predicting ETS concentrations in indoor spaces will be discussed here.

Predictive or exploratory models for indoor concentrations of ETS-associated air contaminants are generally either physical/chemical or statistical in nature. The physical/chemical model usually follows some form of the general mass balance equation. This approach requires detailed information on the input parameters (e.g., ETS source strengths, infiltration rates, mixing, reaction rates) to predict the indoor concentrations. The input parameters are either measured in chamber studies and in homes or are estimated. This approach has been extensively utilized in chamber studies of ETS-associated air contaminants (Repace and Lowrey, 1980; Hoegg, 1972; Leaderer et al., 1984). In one report, the mass balance equation was used to estimate the range of indoor concentrations of RSP associated with ETS over a range of assumptions related to the input parameters (NRC, 1986). The results of that effort are shown in Figures 3-15 and 3-16. (These figures were taken directly from NRC, 1986.) Figures 3-15 and 3-16 allow for the easy calculation of RSP mass from ETS in indoor environments for a range of conditions. These

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figures highlight the large impact of tobacco combustion on indoor RSP levels and indicate that variations in input parameters (e.g., smoking occupancy) can have substantial impacts on predicted RSP levels.

The mass balance model in its original form requires the measurement or estimation of a number of parameters and, hence, is not easily applied to field studies. A condensed version of the mass balance equation for estimating ETS-generated RSP levels in a variety of indoor microenvironments has been developed by using known emission rates of RSP for tobacco combustion in combination with data from several sources, including both measured and estimated parameters (e.g., RSP emission rates, smoking densities, infiltration or ventilation rates, deposition rates)(Leaderer, 1988). The condensed model is given by:

$$C_{eq} = K(D_{hs}/N_v)$$

where: C_{eq} is the equilibrium RSP concentration in a space due to smoking in $\mu g/m^3$; D_{hs} = the number of active smokers (burning cigarettes) per 100 m^3; N_v is the infiltration/ventilation rate for the space in air changes per hour; and K is calculated from standard conditions (smoking rates, RSP emission rates, mixing rates, ventilation rates, and particle loss rates to surfaces) and is equal to 217 for spaces with three or more smokers, 145 for two smokers, and 72 for one smoker (Repace, 1987). The authors of this approach are currently modifying the model to incorporate nicotine measurements (Repace and Lowrey, in preparation). This simplified model offers an easy method to estimate exposures to RSP-associated ETS. While the model has not been fully validated, it does offer an easy method by which RSP-associated ETS in various indoor spaces can be easily estimated.

The second modeling approach is statistical in nature and based on empirical measurements. These models make simple assumptions with little or no transformations of the independent input variables to the model. The statistical models use, as input parameters, data obtained in large field studies through both measurement and estimation (questionnaires). The statistical models are typically simple linear models where the independent variables are used as they are recorded from the questionnaires to explain variations in the concentrations of the air contaminants measured.

The statistical approach has not been widely used. In a study of 96 homes in New York State (Leaderer and Hammond, 1991), measured weekly levels of RSP and vapor phase nicotine were compared to the number of cigarettes reported smoked (obtained by questionnaire), house

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volume, and measured infiltration rates. Respondent-reported number of cigarettes predicted both residential RSP and vapor phase nicotine-associated ETS levels very well (Figure 3-10). The inclusion of house volume and infiltration rate as independent variables in the models occasionally proved to be significant at the 0.05 level, but it explained only a small amount of the variation in the model between measured RSP and nicotine levels.

3.5. SUMMARY

Environmental tobacco smoke is a major source of indoor air contaminants. The ubiquitous nature of ETS in indoor environments indicates that some unintentional inhalation of ETS by nonsmokers is unavoidable. Environmental tobacco smoke is a dynamic complex mixture of more than 4,000 chemicals found in both vapor and particle phases. Many of these chemicals are known toxins and carcinogenic agents. Nonsmoker exposure to ETS-related toxic and carcinogenic substances will occur in indoor spaces where there is smoking occupancy. Many of the ETS compounds are emitted in higher concentrations in sidestream smoke than mainstream smoke. Sidestream emissions, however, are quickly diluted into the environment where ETS exposures take place. Individuals close to smokers (e.g., an infant in a smoking parent's arms) may be directly exposed to the plume of sidestream smoke or exhaled mainstream smoke and thus be more heavily exposed.

Given the complex nature of ETS, it is necessary to identify marker or proxy compounds that, when measured, will allow for the quantification of exposure to ETS. Vapor phase nicotine and respirable suspended particle mass are two such markers that are suitable indicators of exposure to ETS. Nicotine and RSP have been measured in personal monitoring studies and in studies of a variety of indoor environments. The results of these studies clearly demonstrate that reported exposure to ETS, even under the conditions of low frequency, duration, and magnitude, will result in RSP and nicotine values above background levels. These studies indicate that ETS exposures take place in a wide range of microenvironments (e.g., residences, workplaces, restaurants, airplanes) where smoking occurs. Indoor levels of RSP and vapor phase nicotine have been shown to vary in a linear fashion with reported tobacco consumption. Nicotine levels measured indoors have ranged from less than 1 $\mu g/m^3$ to more than 500 $\mu g/m^3$, while RSP-associated ETS levels have ranged from less than 5 $\mu g/m^3$ to more than 1 mg/m^3. Nicotine exposures greater than 100 $\mu g/m^3$ are exceedingly rare; most environments measured have ranged from less than 0.3 $\mu g/m^3$ (smoke free) to 30 $\mu g/m^3$; bars and smoking sections of planes may reach

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50 to 75 $\mu g/m^3$. Thus, the normal range of ETS exposures is approximately hundredfold: 0.3 to 30 $\mu g/m^3$ for nicotine and from 5 to 500 $\mu g/m^3$ for RSP.

In residences with smoking occupancy, average daily or weekly nicotine values might typically range from less than 1 to 10 $\mu g/m^3$, varying principally as a function of number of smokers or number of cigarettes smoked. Average daily or weekly residential concentrations of ETS-associated RSP could be expected to increase from 18 to 95 $\mu g/m^3$ (added to background levels) in homes where smoking occurs. Like nicotine, ETS-associated RSP increases with increased smoking. Average levels of nicotine and RSP in offices with smoking occupancy are roughly comparable to those in homes.

Cotinine in saliva, blood, and urine is the most widely accepted biomarker of ETS exposure. It is not directly related to the air exposure to nicotine because of substantial differences in the time course of exposure uptake, metabolism, and elimination of nicotine in exposed individuals. In addition, the ratio of cotinine in smokers versus nonsmokers may not be the same as the ratio for the active agents in ETS responsible for the adverse effects. Cotinine, however, is an excellent indicator that ETS exposure has taken place and may be a good indicator of dose. The available data indicate that as many as 80% of nonsmokers are exposed to ETS, that there is variability in average exposure levels among different cities, and that cotinine levels vary as a function of passive smoke exposure. Comparisons of cotinine levels in smokers and ETS-exposed nonsmokers have led to estimates that nonsmokers receive from 0.1% to 7% of the dose of nicotine of an average smoker. The dose of active agents may be quite different (e.g., nonsmokers may receive 10% to 20% of the dose of 4-ABP that smokers inhale). These estimates, however, are based on a number of assumptions that may not hold.

Questionnaires are the most commonly used method to assess exposure to ETS in both retrospective studies of acute and chronic effects and in prospective studies. They have been used not only to establish simple categories of ETS exposure, but also to obtain information on activity patterns of exposed individuals and to obtain information on environmental factors affecting concentrations in different indoor environments. No standardized or validated questionnaires have yet been developed for assessing ETS exposure. A number of studies have compared questionnaire responses to measured air concentrations of nicotine and RSP and cotinine levels. These efforts have indicated that a significant percent of individuals reporting no exposure had actually been exposed. In general, questionnaires had moderate success in assessing exposure status and level of exposure. Misclassification errors must be addressed in using questionnaires to assess ETS exposure.

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Physical/chemical and statistical models provide a viable means for predicting concentrations of ETS-related contaminants in situations when it is impractical to obtain direct measurements. The utility of these models will be enhanced when they are better validated.

Environmental tobacco smoke represents an important source of indoor air contaminants. The available data suggest that exposure to ETS is widespread with a wide range of exposure levels.

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Table 3-1. Distribution of constituents in fresh, undiluted mainstream smoke and diluted sidestream smoke from nonfilter cigarettes[1]

Constituent	Amount in MS	Range in SS/MS
Vapor phase:[2]		
Carbon monoxide	10-23 mg	2.5-4.7
Carbon dioxide	20-40 mg	8-11
Carbonyl sulfide	12-42 μg	0.03-0.13
Benzene[3]	12-48 μg	5-10
Toluene	100-200 μg	5.6-8.3
Formaldehyde[4]	70-100 μg	0.1-~50
Acrolein	60-100 μg	8-15
Acetone	100-250 μg	2-5
Pyridine	16-40 μg	6.5-20
3-Methylpyridine	12-36 μg	3-13
3-Vinylpyridine	11-30 μg	20-40
Hydrogen cyanide	400-500 μg	0.1-0.25
Hydrazine[4]	32 ng	3
Ammonia	50-130 μg	3.7-5.1
Methylamine	11.5-28.7 μg	4.2-6.4
Dimethylamine	7.8-10 μg	3.7-5.1
Nitrogen oxides	100-600 μg	4-10
N-Nitrosodimethylamine[4]	10-40 ng	20-100
N-Nitrosodiethylamine[4]	ND-25 ng	<40
N-Nitrosopyrrolidine[4]	6-30 ng	6-30
Formic acid	210-490 μg	1.4-1.6
Acetic acid	330-810 μg	1.9-3.6
Methyl chloride	150-600 μg	1.7-3.3

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Table 3-1. (continued)

Constituent	Amount in MS	Range in SS/MS
Particulate phase:[2]		
Particulate matter[8]	15-40 mg	1.3-1.9
Nicotine	1-2.5 mg	2.6-3.3
Anatabine	2-20 μg	<0.1-0.5
Phenol	60-140 μg	1.6-3.0
Catechol	100-360 μg	0.6-0.9
Hydroquinone	110-300 μg	0.7-0.9
Aniline[4]	360 ng	30
2-Toluidine	160 ng	19
2-Naphthylamine[3]	1.7 ng	30
4-Aminobiphenyl[3]	4.6 ng	31
Benz[*a*]anthracene[5]	20-70 ng	2-4
Benzo[*a*]pyrene[4]	20-40 ng	2.5-3.5
Cholesterol	22 μg	0.9
γ-Butyrolactone[5]	10-22 μg	3.6-5.0
Quinoline	0.5-2 μg	3-11
Harman[6]	1.7-3.1 μg	0.7-1.7
N'-Nitrosonornicotine[5]	200-3,000 ng	0.5-3
NNK[7]	100-1,000 ng	1-4
N-Nitrosodiethanolamine[4]	20-70 ng	1.2
Cadmium[4]	110 ng	7.2
Nickel[3]	20-80 ng	13-30
Zinc	60 ng	6.7
Polonium-210[3]	0.04-0.1 pCi	1.0-4.0
Benzoic acid	14-28 μg	0.67-0.95
Lactic acid	63-174 μg	0.5-0.7
Glycolic acid	37-126 μg	0.6-0.95
Succinic acid	110-140 μg	0.43-0.62

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Table 3-1. (continued)

[1] Data from Elliot and Rowe (1975); Schmeltz et al. (1979); Hoffman et al. (1983); Klus and Kuhn (1982); Sakuma et al. (1983, 1984a,b); Hiller et al. (1982). Diluted SS is collected with airflow of 25 ml/s, which is passed over the burning cone; as presented in the NRC report on passive smoking (1986).

[2] Separation into vapor and particulate phases reflects conditions prevailing in MS and does not necessarily imply same separation in SS.

[3] Known human carcinogen, according to U.S. EPA or IARC.

[4] Probable human carcinogen, according to U.S. EPA or IARC.

[5] Animal carcinogen (Vaino et al., 1985).

[6] 1-methyl-9*H*-pyrido[3,4-*b*]-indole.

[7] NNK = 4-(*N*-methyl-*N*-nitrosamino)-1-(3-pyridyl)-1-butanone.

[8] Contains di- and polycyclic aromatic hydrocarbons, some of which are known animal carcinogens.

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Table 3-2. Studies measuring personal exposure to airborne nicotine associated with ETS for nonsmokers

Study	Setting	Subject	N	Nicotine, $\mu g/m^3$ X(±SD)	Nicotine, $\mu g/m^3$ Range	Comments
Mattson et al., 1989	Airplane	Attendants	16	4.7 (±4.0)	0.1-10.5	4 attendants on 4 flights
Schenker et al., 1990	Railroad	Clerks	40	6.9		Samples collected over work shifts
Coultas et al., 1990a	Workplace	Nonindustrial	15	20.4 (±20.6)		
Muramatsu et al., 1984	Office	Volunteers	10	21.1		Calculated from data presented
	Laboratory		8	5.8		
	Conference room		5	38.7		
	Home		3	11.2		
	Hospital lobby		1	3.0		
	Hotel lobby		4	11.2		
	Restaurant		15	26.0		
	Transportation		22	21.7		
Muramatsu et al., 1984	Office	Volunteers	3	6.9		Calculated from data presented
	Home		7	7.0		
	Restaurant		15	28.2		
	Car		7	40.0		
	Public transportation		1	11.4		

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Table 3-3. Studies measuring personal exposure to particulate matter associated with ETS for nonsmokers

Study	Setting	Number of subjects			Particle Mass, $\mu g/m^3$		Particle Mass due to ETS
		Total	No ETS exp.	ETS exp.	X (±SD)	Range	$\mu g/m^3$
Spengler et al., 1981	24hr day	45			NR	NR	20[a]
Spengler et al., 1985	24hr day	101			NR	NR	
			28		NR	NR	28[a]
				73	NR	NR	
Sexton et al., 1984	24hr day	48			NR	NR	
			NR		31.7	NR	18.4[a]
				NR	50.1	NR	
Coultas et al., 1990a	Workplace	15			63.9±41.5	4.0-145.8	
			1		4.0		64[b]
				14	68.2±39.5	14.7-145.8	
Schenker, 1990	Workplace				86		[c]

a = Calculated by authors from the regression line.
b = Calculated from data presented, after the method of Leaderer and Hammond (1991).
c = Calculated from nicotine exposure, after the method of Leaderer and Hammond (1991).

NR = Not reported

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Table 3-4. Weekly average concentrations of each measure of exposure by parental smoking status in the cross-sectional study, Minnesota, 1989

	Smoking Status				
	Non-smokers	Light smokers	Father only	Mother only	Both parents
Number of subjects	23	4	8	6	7
Total cigarettes (no./week)	0.9	28.8	68.6	58.8	227.6
Activity room nicotine ($\mu g/m^3$)	0.15	0.32	2.45	5.50	12.11
Bedroom nicotine ($\mu g/m^3$)	-	0.30	1.21	2.66	5.32

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Table 3-5. Approximate relations of nicotine as the parameter between nonsmokers, passive smokers, and active smokers[1]

Nicotine/Cotinine	Nonsmokers Without ETS Exposure (N=46)		Nonsmokers With ETS Exposure (N=54)		Active Smokers (N=94)
	Mean Value	% of Active Smokers' Value	Mean Value	% of Active Smokers' Value	Mean Value
Nicotine (ng/ml):					
in plasma	1.0	7.0	0.8	5.5	14.8
in saliva	3.8	0.6	5.5	0.8	673
in urine	3.9	0.2	12.1*	0.7	1,750
Cotinine (ng/ml):					
in plasma	0.8	0.3	2.0*	0.7	275
in saliva	0.7	0.2	2.5**	0.8	310
in urine	1.6	0.1	7.7**	0.6	1,390

[1] Differences between nonsmokers exposed to ETS compared with nonsmokers without exposure: *p<0.01;**p<0.001.

Source: Jarvis, 1987.

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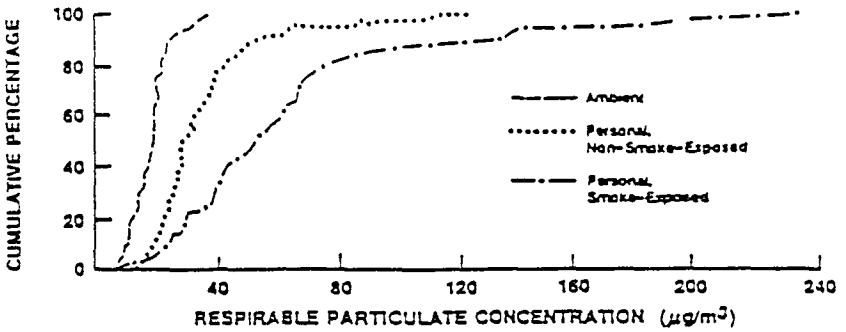

Figure 3-1. Cumulative frequency distribution of respirable suspended particle (RSP) mass concentrations from central site ambient and personal monitoring of smoke-exposed and nonsmoke-exposed individuals. Reprinted from Spengler et al., 1985.

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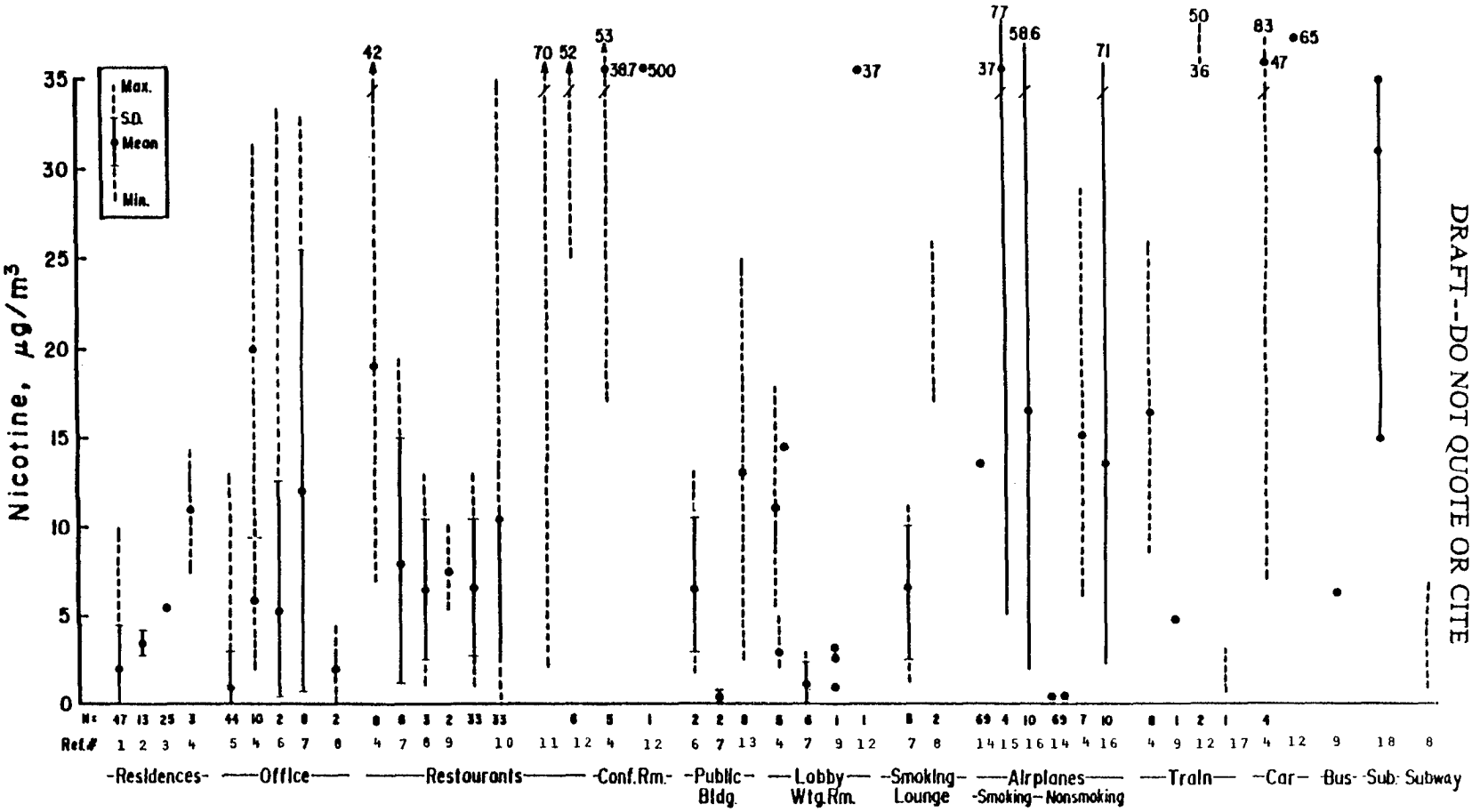

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Figure 3-2. Mean, standard deviation, maximum, and minimum nicotine values measured in different indoor environments with smoking occupancy. References from which observations are reported and the number of environments monitored are also given.

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REFERENCES FOR FIGURES 3-2 AND 3-4

Figure 3-2

1 NRC, 1986
2 U.S. DHHS, 1986
3 Brunnemann et al., 1976
4 Wynder and Hoffmann, 1967
5 Dube and Green, 1982
6 Adams, 1987
7 Guerin, 1987
8 Higgins, 1987
9 Leaderer, 1990
10 NRC, 1981
11 Hammond, 1987
12 Eatough et al., 1986
13 Lofroth et al., 1989
14 Eatough et al., 1989
15 Leaderer and Hammond, 1991
16 Benner et al., 1989
17 Hammond et al., 1988
18 Rickert et al., 1984

Figure 3-4

19 Eudy et al., 1985
20 Eatough et al., 1990
21 Hammond, 1987
22 Hammond, 1987
23 Mumford et al., 1989
24 Hammond et al., 1989
25 Marbury, 1990
26 Eatough, 1989
27 Koutrakis et al., 1989
28 DHEW, 1977
29 Muramatsu et al., 1984
30 Oldaker and Conrad, 1987
31 Ogden et al., 1989
32 Leaderer, 1988
33 Repace and Lowrey, 1980
34 Ishizu, 1980
35 Schenker et al., 1990
36 Coghlin et al., 1989
37 Spengler et al., 1981
38 Spengler et al., 1985
39 Sexton et al., 1984
40 Weber, 1980

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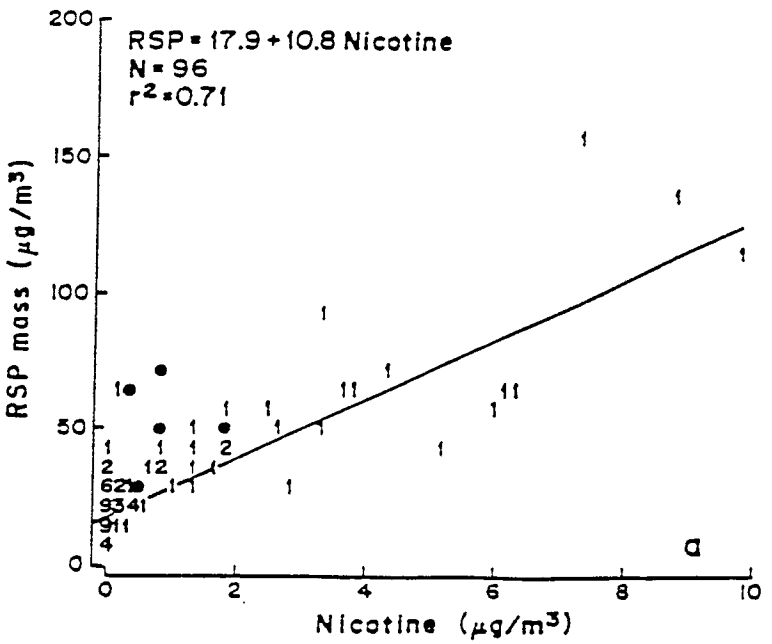

Figure 3-3. Weeklong respirable suspended particle (RSP) mass and nicotine measurements in 96 residences with a mixture of sources. Numbers 1-9 refer to the number of observations at the same concentration. Reprinted from Leaderer and Hammond, 1991.

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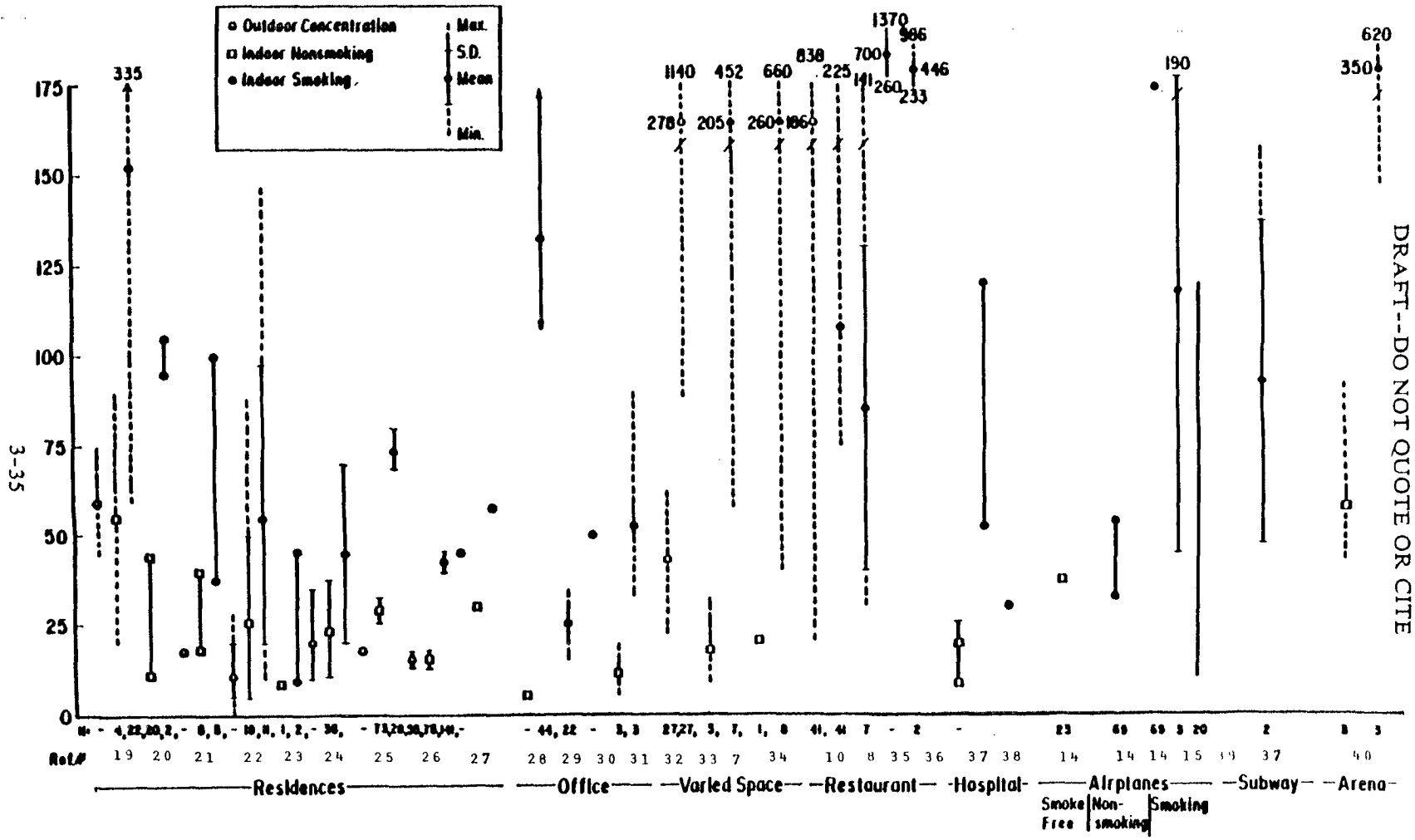

Figure 3-4. Mean, standard deviation, maximum, and minimum concentrations of respirable suspended particle (RSP) mass measured in different indoor environments for smoking and nonsmoking occupancy. Also shown are outdoor concentrations. References from which observations are reported and the number of environments monitored are provided with Figure 3-2.

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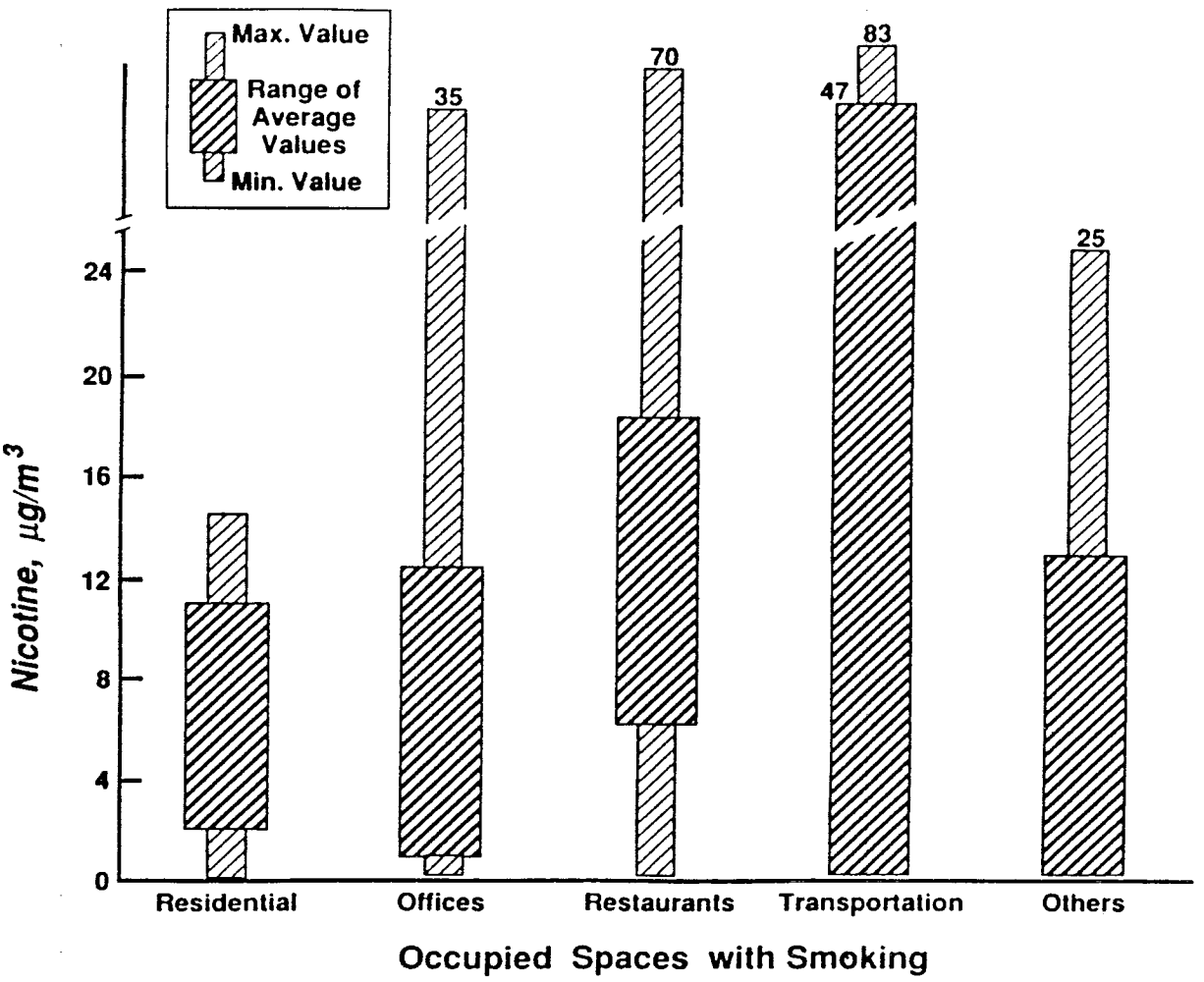

Figure 3-5. Range of average nicotine concentrations and range of maximum and minimum values measured by different indoor environments for smoking occupancy from studies shown in Figure 3-2. Only those studies with sampling times of 4 hours or greater are included in the residential and office indoor environment summaries.

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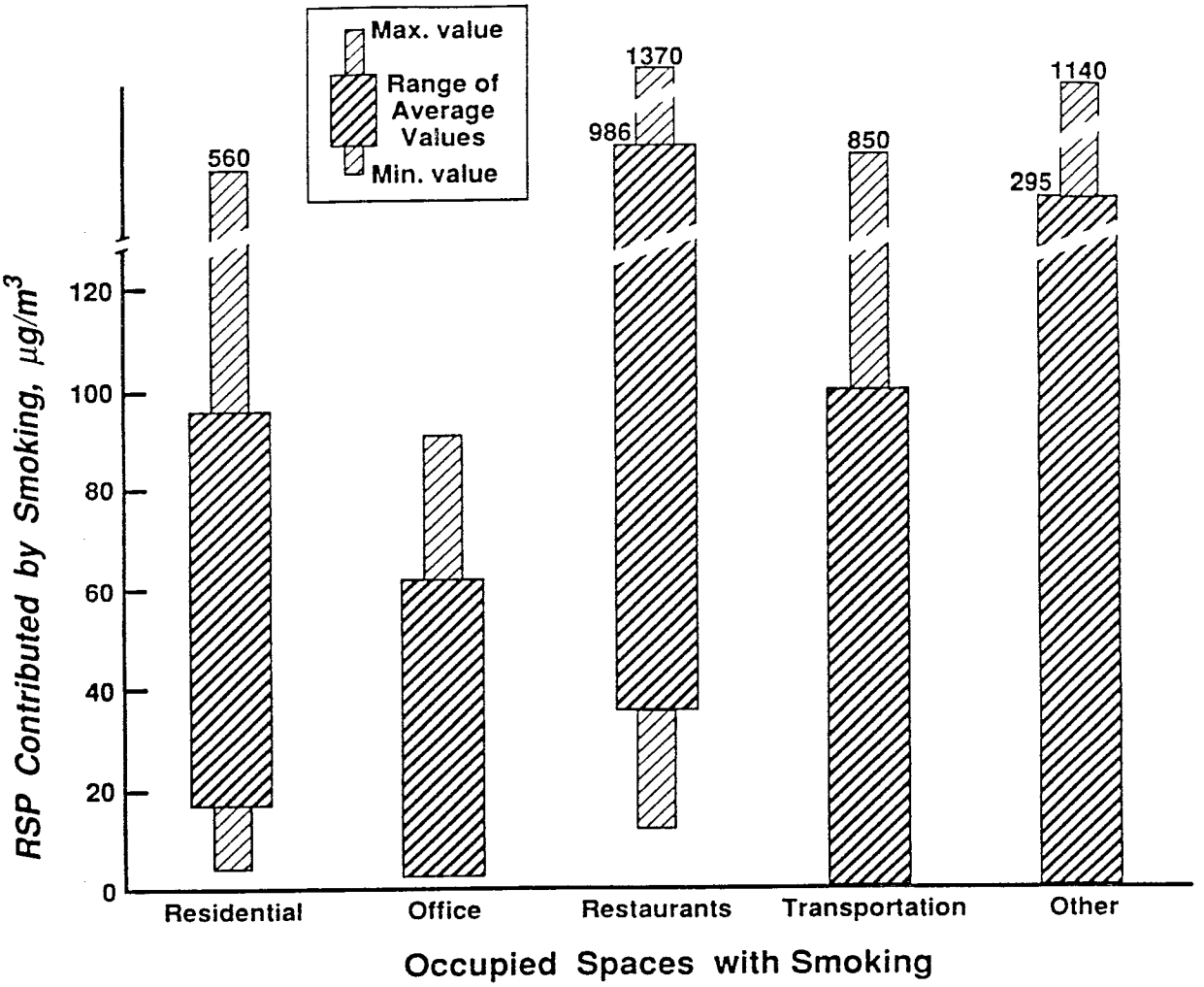

Figure 3-6. Range of average respirable suspended particle (RSP) mass concentrations and range of maximum and minimum values measured by different indoor environments for smoking occupancy from studies shown in Figure 3-4. RSP values represent the contribution to background levels without smoking. Background levels were determined by subtracting reported indoor concentrations without smoking. Only those studies with sampling times of 4 hours or greater are included in the residential and office indoor environment summaries.

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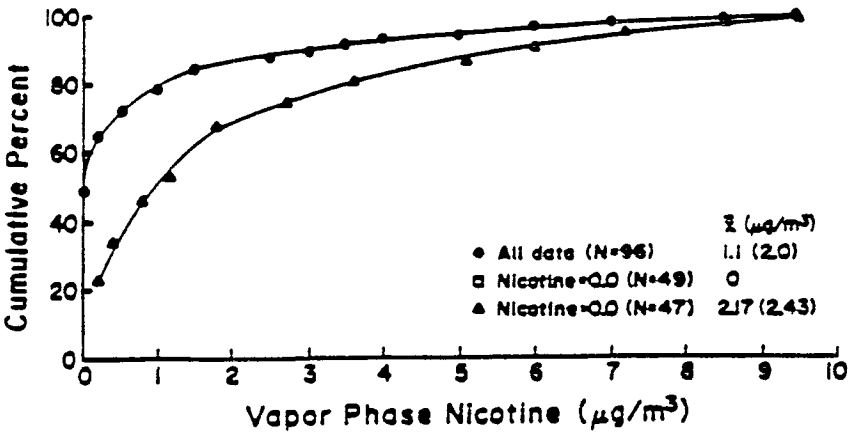

Figure 3-7. Cumulative frequency distribution and arithmetic means of vapor-phase nicotine levels, measured over a 1-week period in the main living area in residences in Onondaga and Suffolk Counties in New York State between January and April 1986. Reprinted from Leaderer and Hammond, 1991.

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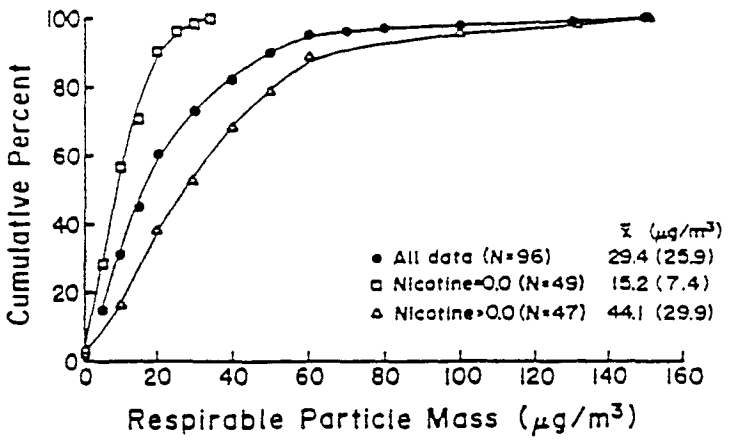

Figure 3-8. Range of average nicotine concentrations and range of maximum and minimum values measured by different indoor environments from studies shown in Figure 3-2. Only those studies with sampling times of 4 hours or greater are included in the residential and office indoor environment summaries.

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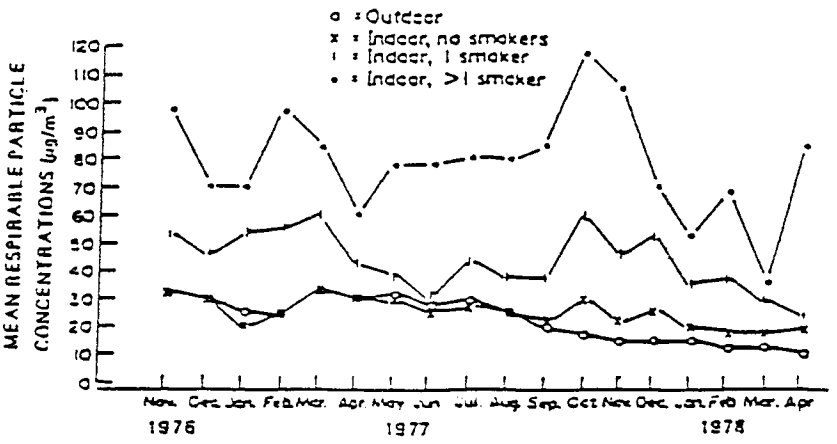

Figure 3-9. Monthly mean respirable suspended particle (RSP) mass concentrations in six U.S. cities. Reprinted from Spengler et al., 1981.

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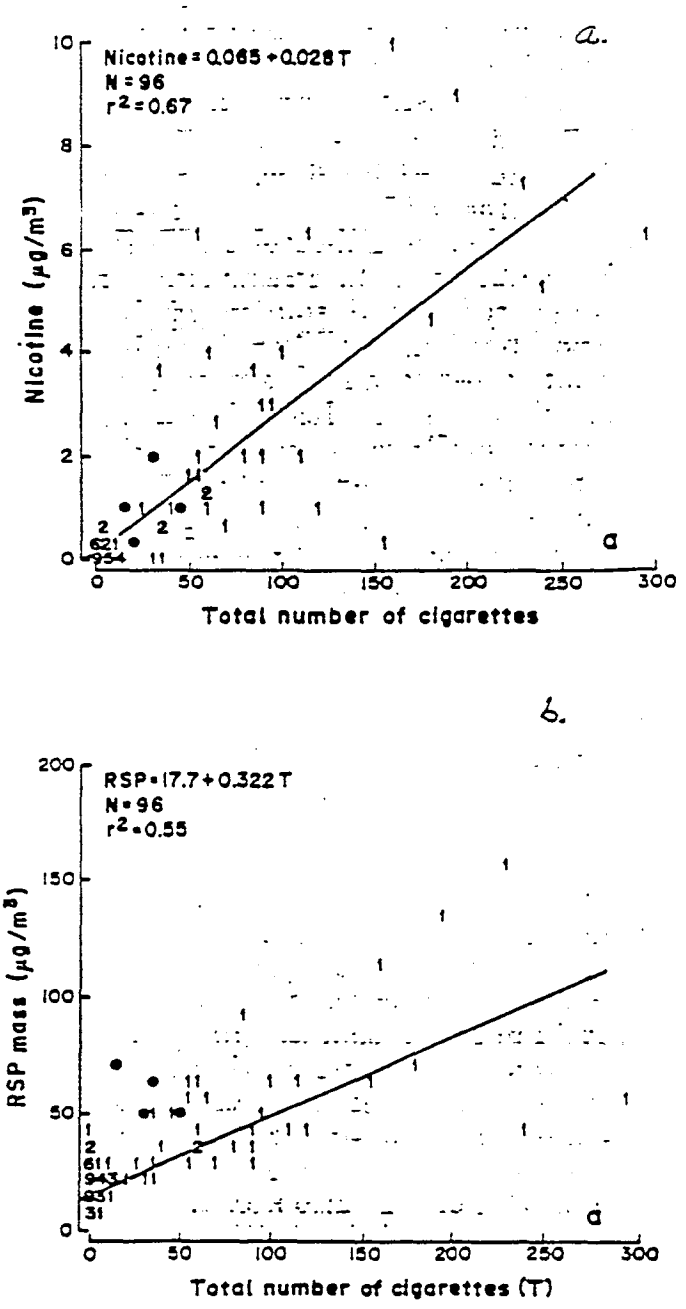

Figure 3-10 a and b. Weeklong nicotine and respirable suspended particle (RSP) mass concentrations, measured in the main living area of 96 residences versus the number of questionnaire-reported cigarettes smoked during the air-sampling period. Numbers 1-9 refer to the number of observations at the same concentrations. Closed circles indicate that cigar or pipe smoking was reported in the houses, with each cigar or pipe smoked set equal to a cigarette. Data from residences in Onondaga and Suffolk counties in New York State between January and April 1986.

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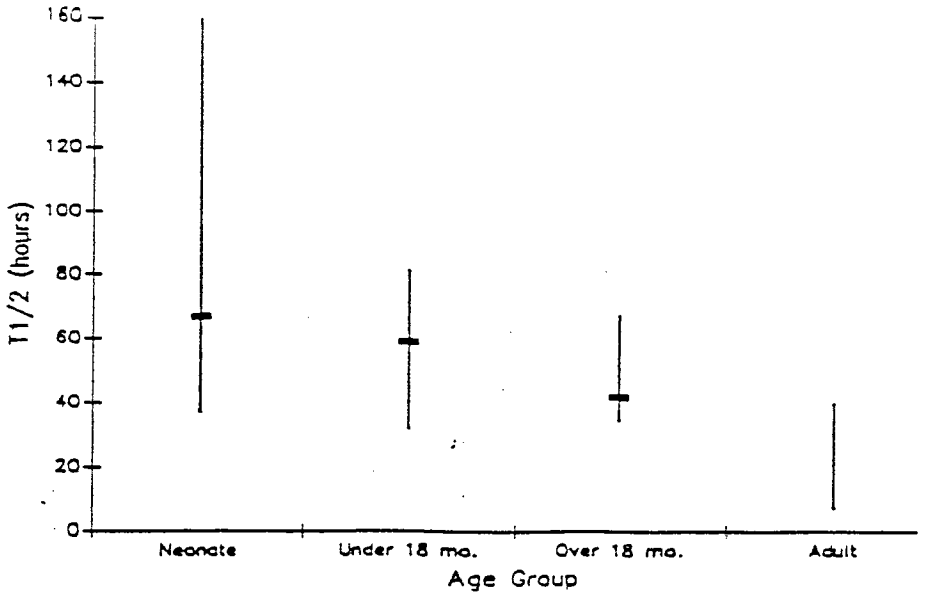

Figure 3-11. Average continue $t_{1/2}$ by age groups. Reprinted from Collier et al., 1990.

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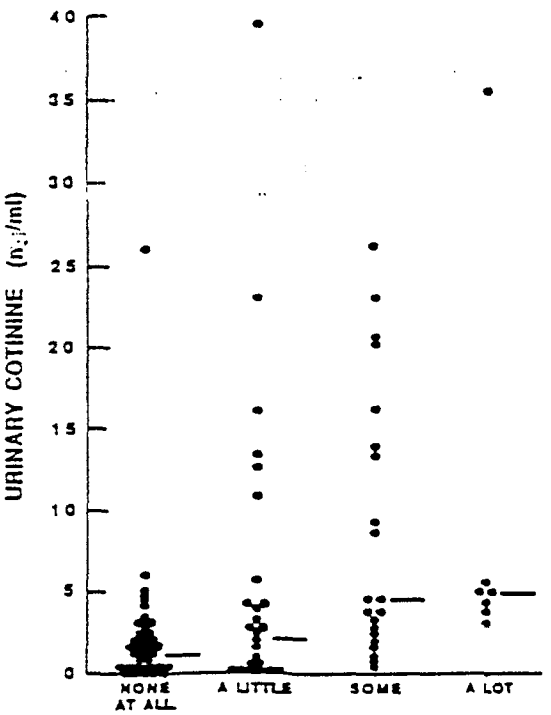

Figure 3-12. Distribution of individual concentrations of urinary cotinine by degree of self-reported exposure to ETS. Horizontal bars indicate median values. Reprinted from Jarvis and Russell[1], 1985.

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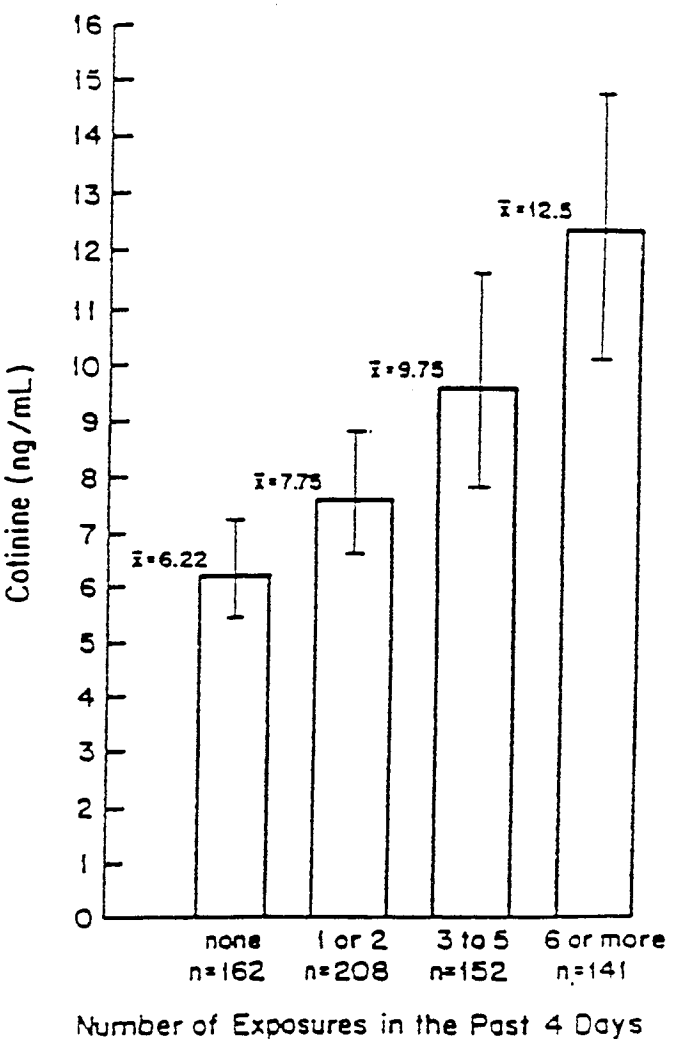

Figure 3-13. Urinary cotinine concentrations by number of reported exposures to tobacco smoke in the past 4 days among 663 nonsmokers, Buffalo, New York, 1986. Reprinted from Cummings et al., 1990.

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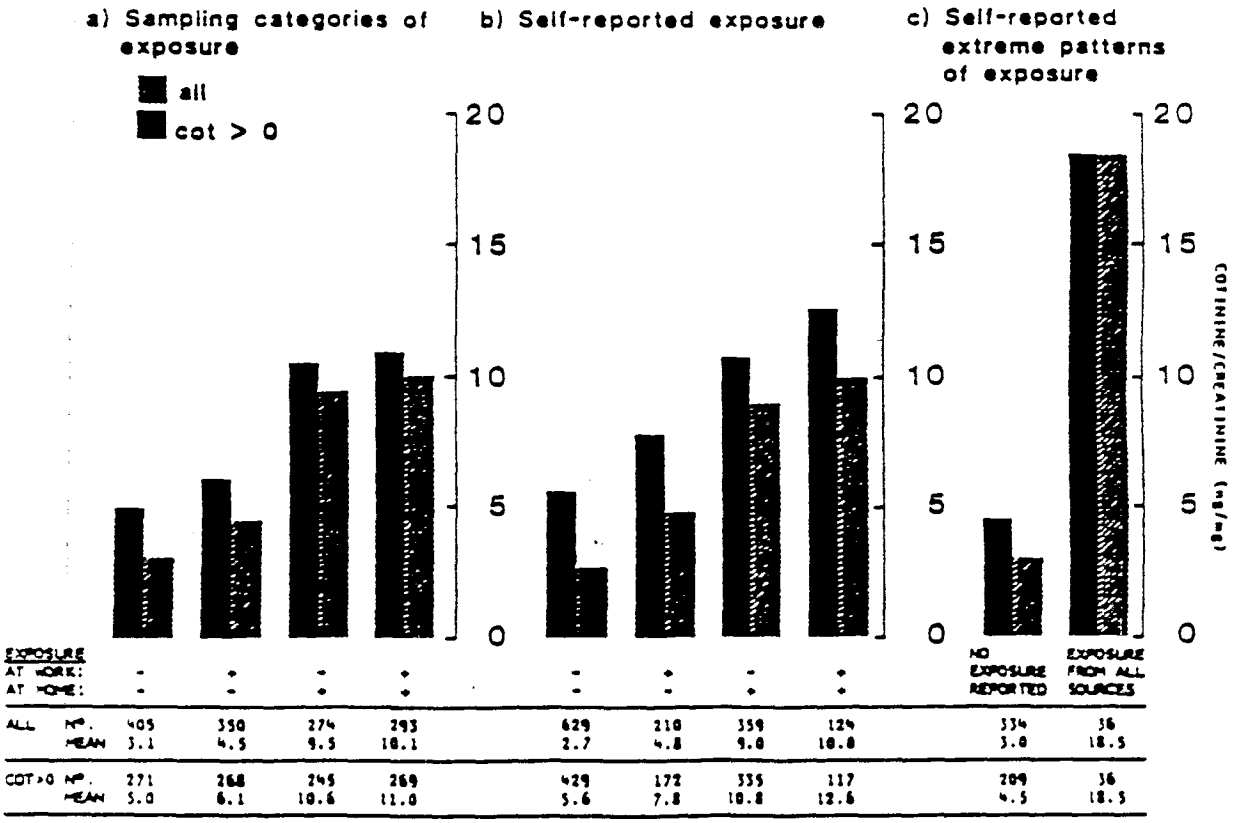

AT WORK:	-	+	-	+	-	+	-	+			
AT HOME:	-	-	+	+	-	-	+	+			
ALL NO.	405	350	274	293	629	218	359	124	334	36
ALL MEAN	3.1	4.5	9.5	10.1	2.7	4.8	9.0	10.0	3.0	18.5
COT>0 NO.	271	268	245	269	429	172	335	117	209	36
COT>0 MEAN	5.0	6.1	10.6	11.0	5.6	7.8	10.8	12.6	4.5	18.5

Figure 3-14. Average cotinine/creatinine levels for subgroups of nonsmoking women defined by sampling categories of exposure or by self-reporting exposure to ETS from different sources during the 4 days preceding collection of the urine sample. Reprinted from Riboli et al., 1990.

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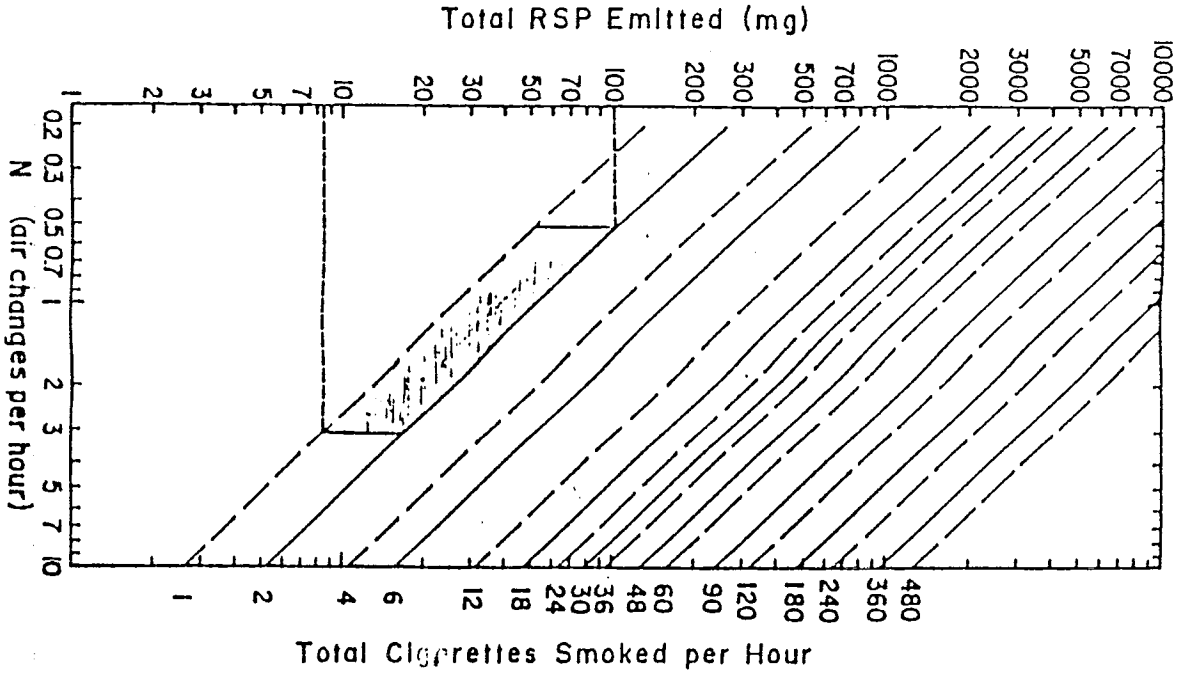

Figure 3-15. Diagram for calculating the respirable suspended particle (RSP) mass from ETS emitted into any occupied space as a function of the smoking rate and removal rate (N). The removal rate is equal to the sum of the ventilation or infiltration rate (n_v) and removal rate by surfaces (N) times the mixing factor m. The calculated ETS-related RSP mass determined from this figure serves as an input to Figure 3-16 to determine the ETS-related RSP mass concentration in any space in ug/m^3. Smoking (diagonal lines) are given as cigarettes smoked per hour. Mixing is determined as a fraction and n_v and n8 are in air changes per hour (ach). All three parameters have to be estimated or measured. Calculations were made using the equilibrium form of the mass-balance equation and assume a fixed emission rate of 26 mg/m^3 of RSP.

Shaded area shows the range of RSP emissions that could be expected for a residence with one smoker smoking at a rate of either 1 or 2 cigarettes per hour for the range of mixing, ventilation, and removal rates occurring in residences under steady-state conditions. Reprinted from NRC (1986).

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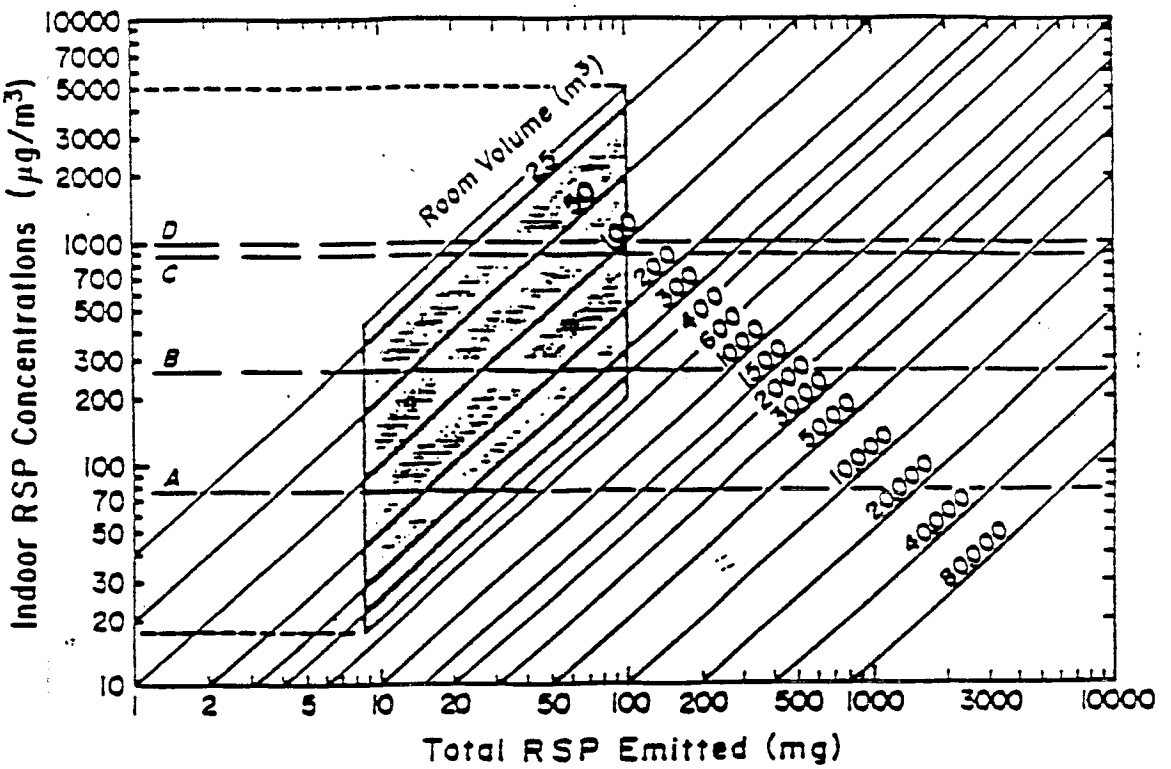

Figure 3-16. Diagram to calculate the ETS-associated respirable suspended particle (RSP) mass concentration in a space as a function of total mass of ETS-generated RSP emitted (determined from Figure 3-15) and the volume of a space (diagonal lines). The concentrations shown assume a background level in the space of zero. The particle concentrations shown are estimates during smoking occupancy. The dashed horizontal lines (A, B, C, and D) refer to National Ambient Air Quality Standards (health-related) for total suspended particulates established by the U.S. Environmental Protection Agency. A is the annual geometric mean. B is the 24-hour value not to be exceeded more than once a year. C is the 24-hour air pollution emergency level. D is the 24-hour significant harm level. Shaded area shows the range of concentrations expected (from Figure 3-15) for a range of typical volumes of U.S. residences and rooms in these residences. Reprinted from NRC (1986).

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4. HAZARD IDENTIFICATION I: LUNG CANCER IN ACTIVE SMOKERS, LONG-TERM ANIMAL BIOASSAYS, AND GENOTOXICITY STUDIES

4.1. INTRODUCTION

Numerous epidemiologic studies have conclusively established that the tobacco smoke inhaled from active smoking is a human lung carcinogen (U.S. DHHS, 1982; IARC, 1986). A clear dose-response relationship exists between lung cancer and amount of exposure, without any evidence of a threshold level. It is, therefore, reasonable to theorize that exposure to environmental tobacco smoke (ETS) might also increase the risk of lung cancer in both smokers and nonsmokers. As documented in the previous chapter, the chemical compositions of mainstream smoke (MS) and ETS are qualitatively similar, and both contain a number of known and suspected human carcinogens. In addition, both MS and ETS have been shown to be carcinogens in animal bioassays (Wynder and Hoffman, 1967; Grimmer et al., 1988) and genotoxins in in vitro systems (IARC, 1986). Furthermore, as the previous chapter also describes, exposure assessments of indoor air and measurements of nicotine levels in nonsmokers confirm that passive smokers are exposed to and absorb appreciable amounts of ETS that might result in notable lung cancer risk.

This chapter reviews the major evidence for the lung carcinogenicity of tobacco smoke derived from human studies of active smoking and the key supporting evidence from animal bioassays and in vitro experiments. The evidence from the few animal and mutagenicity studies pertaining specifically to ETS is also presented. The majority of this information has already been well documented by the U.S. Department of Health and Human Services (U.S. DHHS) (1982) and the International Agency for Research on Cancer (IARC) (1986). The current discussion mainly extracts and summarizes some of the important issues and principal studies described in those excellent reports.

In view of the abundant and consistent human evidence establishing the carcinogenic potential of active smoking to the lung, the bulk of this chapter focuses on the human data. Although EPA's carcinogen risk assessment guidelines (U.S. EPA, 1986a) suggest an extensive review of all evidence pertaining to carcinogenicity, we believe that the wealth of human cancer studies on both MS and ETS provide the most appropriate database from which to evaluate the lung cancer potential of ETS. Thus, the animal evidence and genotoxicity results are given only limited attention here. Similarly, a discussion of the mutagenicity data for individual smoke components would be superfluous in the context of the overwhelming evidence from other, more

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pertinent sources and is not included. Extensive reviews of these data can be found in the U.S. DHHS (1982) and IARC (1986) publications. Claxton et al. (1989) provide an assessment of the genotoxicity of various ETS constituents.

4.2. LUNG CANCER IN ACTIVE SMOKERS

Studies of active smoking in human populations from many countries provide direct and incontrovertible evidence for a dose-related, causal association between cigarette smoking and lung cancer. This evidence includes time trends in lung cancer mortality rates associated with increasing cigarette consumption, high relative risks for lung cancer mortality in smokers of both sexes observed consistently in numerous independent retrospective and prospective studies, and dose-response relationships demonstrated with respect to smoking intensity and duration and for all four major histological types of lung cancer.

4.2.1. Time Trends

While the overall cancer death rate in the United States has been fairly stable since 1950, the lung cancer death rate has increased drastically for both males and females (Figures 4-1 and 4-2). Age-adjusted lung cancer mortality rates in men have increased from 11 per 100,000 in 1940 to 73 per 100,000 in 1982, leveling slightly to 74 per 100,000 in 1987 (Garfinkel and Silverberg, 1991). In women, lung cancer mortality rates have risen from 6 per 100,000 in the early 1960s to 28 per 100,000 in 1987 (Garfinkel and Silverberg, 1991).

The striking time trends and sex differences seen in lung cancer mortality rates correlate with historical smoking patterns. Increases in lung cancer death rates parallel increases in cigarette consumption with a roughly 20-year lag time, accounting for the latency period for the development of smoking-induced lung cancer. Males started smoking cigarettes in large numbers during the years around World War I, whereas females did not begin smoking in appreciable numbers until World War II. Cigarette consumption per capita (based on the total population age 18 and older) in the United States rose from 1,085 in 1925 to a high of 4,148 in 1973. In the past two decades, cigarette consumption has decreased to 2,888 in 1989 (Garfinkel and Silverberg, 1991). This decline correlates with the leveling off of lung cancer mortality rates in recent years.

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4.2.2. Dose-Response Relationships

More than 50 independent retrospective studies have consistently found a dose-related association between smoking and lung cancer (U.S. DHHS, 1982). Eight major prospective studies from five countries corroborate this association:

- American Cancer Society (ACS) Nine-State Study (white males)
  (Hammond and Horn, 1958a,b)
- Canadian War Veterans Study
  (Best et al., 1961; Lossing et al., 1966)
- British Doctors Study
  (Doll and Hill, 1964a,b; Doll and Peto, 1976; Doll et al., 1980)
- American Cancer Society (ACS) 25-State Study
  (Hammond, 1966; Hammond and Seidman, 1980)
- U.S. Veterans Study
  (Kahn, 1966; Rogot and Murray, 1980)
- California Labor Union Study
  (Weir and Dunn, 1970)
- Swedish Study (sample of census population)
  (Cederlof et al., 1975)
- Japanese Study (total population of 29 health districts)
  (Hirayama, 1967, 1975a,b, 1977, 1978, 1982, 1985)

Details of the designs of these studies are summarized in Table 4-1. These eight studies together represent more than 17 million person-years and more than 330,000 deaths. Lung cancer mortality ratios from the prospective studies are presented in Table 4-2. Combining the data from the prospective studies results in a lung cancer mortality ratio of about 10 for male cigarette smokers compared to nonsmokers.

This strong association between smoking and lung cancer is further enhanced by very strong and consistent dose-response relationships. A gradient of increasing risk for lung cancer mortality with increasing numbers of cigarettes smoked per day was established in every one of the prospective studies (Table 4-3). Lung cancer mortality ratios for male smokers who smoked more than 20 cigarettes daily were generally 15 to 25 times greater than those for nonsmokers. Marked increases in lung cancer mortality ratios were also seen in all the lowest dose categories. Males who smoked fewer than 10 cigarettes per day had lung cancer mortality ratios 3 to 10 times

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greater than those for nonsmokers. There is no evidence of a threshold level for the development of smoking-induced lung cancer in any of the studies.

Dose-response relationships with respect to the duration of smoking have also been well established. From the British male physicians study, Peto and Doll (1984) calculated that the excess annual incidence rates of lung cancer after 45, 30, and 15 years of cigarette smoking were in the approximate ratio of 100:20:1 to each other. The California and Swedish studies also demonstrated an increasing risk of lung cancer in men with longer smoking duration (Table 4-4).

Four of the prospective studies examined lung cancer mortality in males by age at initiation of smoking and found increasing risk with younger age (Table 4-5). Some of the studies also investigated smoking cessation in men and observed a decrease in lung cancer risk with increasing number of years since quitting smoking (Table 4-6). The Cancer Prevention Study II, a study of 1,200,000 people in all 50 states, reveals a similar trend for women who quit smoking (Figure 4-3). The occurrence of higher lung cancer mortality ratios in the groups with only a few years since cessation as compared to current smokers (Table 4-6 and Figure 4-3) is attributable to the inclusion of recent ex-smokers who were forced to stop smoking because they already had smoking-related symptoms or illness (U.S. DHHS, 1990). The demonstration of increasing lung cancer risks the younger the age of smoking commencement and decreasing risks with time since smoking cessation establishes the initiation and promotion capabilities of tobacco smoke.

Additional dose-response relationships have been derived from consideration of the types of tobacco products used. Pipe and cigar smokers, who inhale less deeply than cigarette smokers, have lower risks of lung cancer than cigarette smokers (Table 4-7). Furthermore, the American Cancer Society 25-State Study found decreased risks for lung cancer in males and females who smoked cigarettes with lower tar and nicotine content compared to those who smoked cigarettes with higher tar and nicotine content (Table 4-8), although these decreased risks are still substantially higher than the risk to nonsmokers. Similarly, it has been established that smokers of filtered cigarettes have relatively lower lung cancer risks than smokers of nonfiltered cigarettes (Table 4-9). Filters reduce the amount of tars, and hence a portion of the carcinogenic agents, in the MS inhaled by the smoker. Passive smokers, however, do not share in any benefit derived from cigarette filters (see Chapter 3) and may, in fact, be exposed to more ETS if smokers of filtered cigarettes smoke a greater number of cigarettes to compensate for any reduction in nicotine uptake resulting from the filters (U.S. DHHS, 1986).

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4.2.3. Histological Types of Lung Cancer and Associations With Smoking

A number of epidemiologic studies have also examined the association between various histological types of lung cancer and smoking. The results of some of these investigations are summarized in Table 4-10. Problems in interpreting the results of such studies include differences in the nomenclature, criteria, and verification of tumor classification; inadequacy of some specimens, and the small size of many of the patient groups, resulting in unstable risk estimates, particularly in women. There are four major histological types of lung cancer: squamous-cell carcinoma, small-cell carcinoma, adenocarcinoma, and large-cell undifferentiated carcinoma. Sometimes two broad categories--Kreyberg Group I, containing squamous-cell and small-cell carcinomas, and Kreyberg Group II, containing all other epithelial lung cancers, including adenocarcinomas and large-cell undifferentiated carcinomas--are used for classification. The majority of the studies demonstrate an increase in the risk for lung cancer with increasing amount smoked for all four major histological groups in both males and females. The slope of the gradient for adenocarcinomas, however, is shallower than the slopes for the other types.

4.2.4. Proportion of Risk Attributable to Active Smoking

Table 4-11 presents data on the proportion of lung cancer deaths attributable to smoking in various countries. Differences by sex and between countries largely correlate with differences in the proportion of smokers within these populations and the duration and intensity of cigarette usage. In the early 1960s, 50% of U.S. men and 30% of U.S. women smoked, although these proportions have been declining in recent years (Garfinkel and Silverberg, 1991).

In the United States, deaths from lung cancer currently represent one quarter of all cancer deaths. The American Cancer Society predicts there will be 143,000 lung cancer deaths in 1991 (Garfinkel and Silverberg, 1991). Over 85% of this lung cancer mortality is estimated to be attributable to tobacco smoking. In other words, the overwhelming majority of lung cancer deaths, which are a significant portion of all cancer deaths, result from smoking. The strong association between smoking and lung cancer and the dose-response relationships, with effects observable at low doses and no evidence of a threshold, make it highly plausible that passive smoking also causes lung cancer in humans.

4.3. LIFETIME ANIMAL STUDIES

The human evidence for the carcinogenicity of tobacco smoke is corroborated in experimental animal bioassays. The main animal evidence is obtained from inhalation studies in

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the hamster, intrapulmonary implantations in the rat, and skin painting in the mouse. There are no lifetime animal inhalation studies of ETS; however, the carcinogenicity of ETS condensates has been demonstrated in intrapulmonary implantations and skin painting experiments.

Negative responses in short term animal studies (e.g., 60 to 90 days) are not reliable indicators of the carcinogenic potential of a compound because of the long latency period for cancer development. Long-term animal studies at or near the maximum tolerated dose level are used to ensure an adequate power for the detection of carcinogenic activity (U.S. EPA, 1986a).

4.3.1. Inhalation Studies

Although evidence of the carcinogenicity of cigarette smoke originated in humans, attempts were made to develop an inhalation model for smoking in experimental animals in order to study the carcinogenicity of various tobacco products. Such inhalation studies are difficult to conduct, however, because laboratory animals are reluctant to inhale cigarette smoke and will adopt shallow breathing patterns in response to aerosols and irritants. Furthermore, rodents are obligatory nose-breathers, and the anatomy and physiology of the respiratory tract and the biochemistry of the lung differ between rodents and humans. Because of these distinctions, laboratory animals and humans are likely to have different deposition and exposure patterns for the various cigarette smoke components in the respiratory system. For example, rodents have extensive and complex nasal turbinates where significant particle deposition could occur, decreasing exposure to the lung.

The Syrian golden hamster has been the most useful animal inhalation model found so far for studying smoking-induced carcinogenesis. It is more tolerant of tobacco smoke than mice and rats and is relatively resistant to respiratory infections. The hamster also has a low background incidence of spontaneous pulmonary tumors and is, in fact, refractory to the induction of lung cancers by known carcinogenic agents. The inhalation of tobacco smoke by the hamster does, however, induce carcinomas of the larynx. In one study (Dontenwill et al., 1973), three groups of 80 male and 80 female Syrian golden hamsters were exposed for 10 minutes to air-diluted cigarette smoke (1:15) once, twice, or three times daily, 5 days per week, for their lifetimes. Pre-invasive carcinomas of the upper larynx were detected in 11.3%, 30%, and 30.6% of the animals, respectively, and invasive carcinomas were found in 0.6%, 10.6%, and 6.9%, respectively. No laryngeal tumors were observed in control animals. In another experiment, exposure for 59 to 80 weeks to a 11% or 22% cigarette smoke aerosol twice daily for 12 minutes resulted in laryngeal carcinomas in 3 of 44 and 27 of 57 animals, respectively, providing some evidence of a dose-

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response relationship for the induction of carcinoma of the larynx by cigarette smoke (Bernfeld et al., 1979). Bernfeld et al. suggest that the greater deposition of tar per unit of surface area in the larynx compared to the lung may explain the high yield of laryngeal cancers and lack of lung tumors in this animal model.

4.3.2. Intrapulmonary Implantations of Cigarette Smoke Condensates

Because of the difficulties with inhalation studies of cigarette smoke, some in vivo studies examine the carcinogenicity of cigarette smoke condensate (CSC) collected from smoking machines. CSC assays may not, however, reveal all of the carcinogenic activity of actual cigarette smoke, since these condensates lack most of the volatile and semivolatile components of whole smoke. In lifetime rat studies, intrapulmonary implants of CSC in a lipid vehicle cause a dose-dependent increase in the incidence of lung carcinomas (Stanton et al., 1972; Dagle et al., 1978).

ETS condensates have also demonstrated carcinogenicity when implanted into rat lungs (Grimmer et al., 1988). (Actually, only sidestream smoke was examined, but this constitutes roughly 85% of ETS [Fielding, 1985].) Sidestream smoke (SS) emitted by a smoking machine was separated into condensate fractions containing the semivolatiles, the polycyclic aromatic hydrocarbon (PAH)-free particulates and the PAHs with two or three rings, or the PAHs with four or more rings. These fractions were implanted into female Osborne-Mendel rats, following the procedure of Stanton et al. (1972), at a dose level of one cigarette per animal. At the end of the lifetime study, none of the 35 rats in each of the untreated control, vehicle control, or semivolatile-exposed groups had lung carcinomas. In the group exposed to the fraction containing PAH-free particulates and PAHs with two or three rings, there was 1 lung carcinoma in 35 animals. In the group exposed to the fraction comprising PAHs with four or more rings, there were 5 lung carcinomas in 35 rats. An additional group that was exposed to a dose of 0.03 mg benzo[a]pyrene (BaP) per rat exhibited 3 lung carcinomas in 35 animals. The condensate fraction containing BaP and the other PAHs with four or more rings from the SS generated by a single cigarette contains about 100 ng of BaP. Assuming a linear, nonsynergistic dose-response relationship, this would suggest that less than 1% of the total carcinogenicity of that CSC fraction can be attributed to the BaP present in the smoke.

4.3.3. Mouse Skin Painting of Cigarette Smoke Condensates

In addition, numerous studies have shown that when CSC suspended in acetone is chronically applied to mouse skin, significant numbers of the mice develop papillomas or

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carcinomas at the site of application (e.g., Wynder et al., 1957; Davies and Day, 1969). Mouse skin studies have also demonstrated that CSC has both tumor-initiating and tumor-promoting capabilities (Hoffman and Wynder, 1971).

One mouse skin painting study examined the carcinogenicity of ETS condensate (Wynder and Hoffman, 1967). Cigarette tar from SS deposited on the funnel of a smoking machine was suspended in acetone and administered to mouse skin. Fourteen of thirty mice developed skin papillomas, and 3 of 30 developed carcinomas. In a parallel assay in the same study, a suspension of MS condensate applied to deliver a comparable amount of condensate to the skin of 100 mice yielded benign skin tumors in 24 and malignant tumors in 6 of the mice. This suggests that the condensate of SS has greater mouse skin tumorigenicity per unit weight than that of MS.

4.4. GENOTOXICITY

Supportive evidence for the carcinogenicity of tobacco smoke is provided by the demonstration of genotoxicity in numerous short-term assays. Extensive reviews of these studies can be found in IARC (1986) and DeMarini (1983), and only the highlights are presented here. A few studies deal with whole smoke, but most examine CSC. Tobacco smoke is genotoxic in virtually every in vitro system tested, providing overwhelming supportive evidence for its carcinogenic potential.

In *Salmonella typhimurium*, for example, Basrur et al. (1978) found that whole smoke and smoke condensates from various types of tobacco were mutagenic in the presence of a metabolic activating system. SS (Ong et al., 1984) and extracts of ETS collected from indoor air (Lofroth et al., 1983; Alfeim and Randahl, 1984; Lewtas et al., 1987; Ling et al., 1987; Lofroth et al., 1988) also exhibit mutagenic activity in this bacterium. Claxton et al. (1989) found that SS accounted for approximately 60% of the total *S. typhimurium* mutagenicity per cigarette--40% from the ETS particulates and 20% from the ETS semivolatiles. The highly volatile fraction, from either MS or SS, was not mutagenic.

Similarly, cigarette smoke produced mitotic gene conversion, reverse mutation, and reciprocal mitotic recombination in fungi (Gairola, 1982). In addition, CSCs induce mutations, sister chromatid exchanges, and cell transformation in various mammalian cells in culture. Putnam et al. (1985) demonstrated dose-dependent increases in sister chromatid exchange frequencies in bone-marrow cells of mice exposed to cigarette smoke for 2 weeks.

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4.5. SUMMARY AND CONCLUSIONS

The unequivocal causal association between tobacco smoking and lung cancer in humans with dose-response relationships extending down to the lowest observed exposures, as well as the corroborative evidence of the carcinogenicity of both MS and ETS provided by animal bioassays and in vitro studies, clearly establish the plausibility that ETS is also a human lung carcinogen. Furthermore, biomarker studies verify that passive smoking results in detectable uptake of tobacco smoke constituents by nonsmokers, affirming that ETS exposure is a public health concern (Chapter 3).

Active smoking induces squamous-cell carcinomas, small-cell carcinomas, large-cell carcinomas, and adenocarcinomas in humans, all in a dose-related manner. Lung cancer mortality rates have increased dramatically over the past 60 years in males and, more recently, in females, with increasing cigarette consumption. High relative risks for lung cancer, associated with the number of cigarettes smoked per day, have been demonstrated in countless studies, with no evidence of a threshold level of exposure. Dose-response relationships have also been established with respect to duration of smoking. Lung cancer risk increases the younger the age at initiation of smoking and decreases the longer the time since cessation of smoking. These latter trends, coupled with the evidence from mouse skin painting studies, show that tobacco smoke has both tumor-initiating and tumor-promoting capabilities.

Inhalation studies in hamsters confirm that tobacco smoke is carcinogenic to the respiratory tract. In addition, mouse skin painting experiments and intrapulmonary implantations in rats have demonstrated the carcinogenicity of condensates from both MS and ETS. Numerous genotoxicity tests contribute supporting evidence for the carcinogenic potential of cigarette smoke and smoke condensates. The mutagenicity of ETS and its extracts has also been established. As discussed in Chapter 3, MS and ETS are qualitatively similar in composition, and both contain a number of known and suspected human carcinogens.

In fact, these observations alone--the dose-related association between tobacco smoking and lung cancer in humans, which extends to the lowest reported doses; the chemical similarity between MS and ETS; and the confirmation of the carcinogenicity of MS and ETS in animal and in vitro experiments--are sufficient to establish weight-of-evidence for the carcinogenicity of ETS to humans. According to EPA's *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 1986a), a Group A (known human) carcinogen designation is used "when there is sufficient evidence from epidemiologic studies to support a causal association between exposure to the

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agents and cancer." The *Guidelines* establish "three criteria (that) must be met before a causal association can be inferred between exposure and cancer in humans:

1. There is no identified bias that could explain the association.
2. The possibility of confounding has been considered and ruled out as explaining the association.
3. The association is unlikely to be due to chance."

Given the strong dose-related associations with high relative risks consistently observed across numerous independent studies from several countries and the biological plausibility provided by ancillary evidence of the genotoxicity and animal carcinogenicity of MS and by knowledge of the existence of specific carcinogenic components within MS, confounding, bias, and chance can all be ruled out as possible explanations for the observed association between active smoking and lung cancer. Therefore, under the EPA carcinogen classification system, MS would be a Group A (known human) carcinogen, and, due to the similarity in chemical composition between MS and ETS and the known human exposure to ETS (Chapter 3), ETS would also be classified as a known human carcinogen.

In addition, however, there exists a whole body of evidence dealing specifically with human exposure to ETS. Substantial epidemiologic evidence demonstrates increased risks of lung cancer in nonsmokers exposed to actual ambient levels of ETS. Therefore, unlike with many environmental hazards where extrapolation from high-dose animal bioassays or high-level, generally occupational, human exposures must be used to estimate the human risk at environmental levels of exposure, the health risk of ETS exposure can be examined directly from the epidemiologic data. The epidemiologic evidence for the human lung carcinogenicity associated specifically with ETS is the subject of Chapter 5.

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Table 4-1. Main characteristics of major cohort studies on the relationship between smoking and cancer

Study	Year of enrollment	Sample size; initial samples; in brackets, population for follow-up	Source of information on smoking (proportion of respondents)	Duration of follow-up and no. of deaths	Completeness of follow-up for mortality
ACS Nine-state study	1952	204,547 men [187,783]	Self-administered questionnaire	44 months 11,870 deaths	98.9%
Canadian veterans study	1955-1956	207,397 subjects (aged 30+) [92,000]	Self-administered questionnaire (57% respondents)	6 years 9,491 deaths in men; 1,794 deaths in women	NA
British doctors study	1951	34,440 men (aged 20+)	Self-administered questionnaire (69% respondents)	20 years 10,072 deaths	99.7%
		6,194 women (aged 20+)	Self-administered questionnaire (60% respondents)	22 years 1,094 deaths	99%
ACS 25-state study *	1959-1960	1,078,894 subjects First follow-up: 440,558 men, 562,671 women (aged 35-84); second follow-up: 358,422 men, 483,519 women	Self-administered questionnaire	4.5 + 5 years 26,448 deaths in men; 16,773 deaths in women	97.4% in women 97.9% in men in first follow-up
U.S. veterans study	1954	293,958 men (aged 31-84) [248,046]	Self-administered questionnaire (85% respondents)	16 years 107,563 deaths	Almost 100% ascertainment of vital status; 97.6% of death certificates retrieved

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Table 4-1. (continued)

Study	Year of enrollment	Sample size; initial samples; in brackets, population for follow-up	Source of information on smoking (proportion of respondents)	Duration of follow-up and no. of deaths	Completeness of follow-up for mortality
Californian study	1954-1957	68,153 men (aged 35-64)	Self-administered questionnaire	5-8 years 4,706 deaths	NA
Swedish study	1963	27,342 men, 27,732 women (aged 18-69)	Self-administered questionnaire (89% respondents)	10 years 5,655 deaths (2,968 autopsies)	NA
Japanese study	1965	122,261 men, 142,857 women (aged 40+)	Interview (95% of population in area)	16 years 51,422 deaths	Total

NA = not available.

Source: IARC, 1986.

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Table 4-2. Lung cancer mortality ratios--prospective studies

Population	Size	Number of Deaths	Nonsmokers	Cigarette Smokers
British doctors study	34,000 males 6,194 females	441 27	1.00 1.00	14.0 5.0
Swedish study	27,000 males 28,000 females	55 8	1.00 1.00	7.0 4.5
Japanese study	122,000 males 143,000 females	940 304	1.00 1.00	3.76 2.03
ACS 25-State study	358,000 males 483,000 females	2,018 439	1.00 1.00	8.53 3.58
U.S. veterans	290,000 males	3,126	1.00	11.28
Canadian veterans	78,000 males	331	1.00	14.2
ACS 9-state study	188,000 males	448	1.00	10.73
California males in 9 occupations	68,000 males	368	1.00	7.61

Source: U.S. DHHS, 1982.

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Table 4-3. Lung cancer mortality ratios for men and women, by current number of cigarettes smoked per day--prospective studies

Population	Men		Women	
	Cigarettes smoked per Day	Mortality ratios	Cigarettes smoked per day	Mortality ratios
ACS 25-state study	Nonsmoker	1.00	Nonsmoker	1.00
	1-9	4.62	1-9	1.30
	10-19	8.62	10-19	2.40
	20-39	14.69	20-39	4.90
	40+	18.71	40+	7.50
British doctors study	Nonsmoker	1.00	Nonsmoker	1.00
	1-14	7.80	1-14	1.28
	15-24	12.70	15-24	6.41
	25+	25.10	25+	29.71
Swedish study	Nonsmoker	1.00	Nonsmoker	1.00
	1-7	2.30	1-7	1.80
	8-15	8.80	8-15	11.30
	16+	13.70	16+	--
Japanese study (all ages)	Nonsmoker	1.00	Nonsmoker	1.00
	1-19	3.49	< 20	1.90
	20-39	5.69	20-29	4.20
	40+	6.45		
U.S. veterans study	Nonsmoker	1.00		
	1-9	3.89		
	10-20	9.63		
	21-39	16.70		
	≥ 40	23.70		
ACS 9-state study	Nonsmoker	1.00		
	1-9	8.00		
	10-20	10.50		
	20+	23.40		
Canadian veterans	Nonsmoker	1.00		
	1-9	9.50		
	10-20	15.80		
	20+	17.30		
California males in nine occupations	Nonsmoker	1.00		
	about ½ pk	3.72		
	about 1 pk	9.05		
	about 1½ pk	9.56		

Source: U.S. DHHS, 1982.

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Table 4-4. Relationship between risk of lung cancer and duration of smoking in men, based on available information from cohort studies

Reference	Duration of smoking (years)	Standardized mortality ratio (no. of observed deaths)	Approximate annual excess death rate (%)
Weir & Dunn (1970)	1-9	1.13	0.002 (0.001)
	10-19	6.45	0.09 (0.05)
	20+	8.66	0.12 (0.08)
	nonsmokers	1.0	0
Cederlöf et al. (1975)	1-29	1.8 (5)	0.01 (0.008)
	>30	7.4 (23)	0.1 (0.06)
	nonsmokers	1.0 (7)	0

The mortality ratio among nonsmokers was assumed to be 15.6/100,000 per year, as in the American Cancer Society 25-state study. Figures in parentheses were computed by the IARC working group, applying the British doctors' mortality rate among nonsmokers (10.0/100,000 per year).

Source: IARC, 1986.

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Source: https://www.industrydocuments.ucsf.edu/docs/rsdl0000

Table 4-5. Lung cancer mortality ratios for males, by age of smoking initiation--prospective studies

Study	Age of smoking initiation in years	Mortality ratio
ACS 25-state study	Nonsmoker	1.00
	25+	4.08
	20-24	10.08
	15-19	19.69
	Under 15	16.77
Japanese study	Nonsmoker	1.00
	25+	2.87
	20-24	3.85
	Under 20	4.44
U.S. veterans	Nonsmoker	1.00
	25+	5.20
	20-24	9.50
	15-19	14.40
	Under 15	18.70
Swedish study	Nonsmoker	1.00
	19+	6.50
	17-18	9.80
	Under 16	6.40

Source: U.S. DHHS, 1982

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Table 4-6. Relationship between risk of lung cancer and number of years since stopping smoking, in men, based on available information from cohort studies

Reference	No. of years since stopping smoking	Mortality ratio (no. of observed deaths)
ACS 25-state study (Hammond, 1966)	1-19 cig./day	
	Current smokers	6.5 (80)
	<1	7.2 (3)
	1-4	4.6 (5)
	5-9	1.0 (1)
	10+	0.4 (1)
	Nonsmokers	1.0 (32)
	20+ cig./day	
	Current smokers	13.7 (351)
	<1	19.1 (33)
	1-4	12.0 (33)
	5-9	7.2 (32)
	10+	1.1 (5)
	Nonsmokers	1.0 (32)
Swedish study (Cederlöf et al., 1975)	<10	6.1 (12)
	>10	1.1 (3)
	Nonsmokers	1.0 (7)
British doctors study (Doll & Peto, 1976)	Current smokers	15.8 (123)
	1-4	16.0 (15)
	5-9	5.9 (12)
	10-14	5.3 (9)
	15+	2.0 (7)
	Nonsmokers	1.0 (7)
Rogot & Murray (1980)	Current smokers	11.3 (2609)
	<5	18.8 (47)
	5-9	~7.5 (86)
	10-14	~5.0 (100)
	15-19	~5.0 (115)
	20+	2.1 (123)
	Nonsmokers	1.0 NA

NA = not available.

Source: IARC, 1986.

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Source: https://www.industrydocuments.ucsf.edu/docs/rsdl0000

Table 4-7. Relative risks of lung cancer in some large cohort studies among men smoking cigarettes and other types of tobacco

Study	Smoking category	Relative risk	Death rate per 100,000	No. of cases
ACS Nine-state study[1]	Never smoked	1.0	12.8	15
	Occasionally only	1.5	19.2	8
	Cigarettes only	9.9	27.2	249
	Cigars only	1.0	13.1	7
	Pipes only	3.0	38.5	18
	Cigarettes + other	7.6	97.7	148
	Cigars + pipes	0.6	7.3	3
Canadian veterans study	Nonsmokers	1.0		7
	Cigarettes only	14.9		325
	Cigars only	2.9		2
	Pipe only	4.4		18
	Ex-smokers	6.1		18
ACS 25-state study[1]	Never smoked	1.0	12	49
	Cigarettes only	9.2	111	719
	Cigars only	1.9	22	23
	Pipes only	2.2	27	21
	Cigarettes + other	7.4	89	336
	Cigars + pipes	0.9	11	11
Swedish study[1]	Nonsmokers	1.0		7
	Cigarettes only	7.0		28
	Cigarettes + pipe	10.9		27
	Pipe only	7.1		31
	Cigars only	9.2		6
	Ex-smokers	6.1		12

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Table 4-7. (continued)

Study	Smoking category	Relative risk	Death rate per 100,000	No. of cases
British doctors study	Nonsmokers	1.0	10	
	Current smokers	10.4	104	
	Cigarettes only	14.0	140	
	Pipes and/or cigars only	5.8	58	
	Cigarettes + other	8.2	82	
	Ex-smokers	4.3	43	
U.S. veterans study[1]	Nonsmokers	1.0		2609
	Cigarettes	11.3		1095
	Cigarettes only	12.1		41
	Cigars only	1.7		32
	Pipes only	2.1		517
	Ex-cigarette smokers	4.0		
Norwegian study[1]	Nonsmokers	1.0		7
	Cigarettes	9.7		88
	Cigarettes only	9.5		70
	Pipes or cigars only	2.6		12
	Ex-smokers	2.8		11

[1]Figures given in original report.

Source: IARC, 1986.

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Source: https://www.industrydocuments.ucsf.edu/docs/rsdl0000

Table 4-8. Age-adjusted lung cancer mortality ratios for males and females, by tar and nicotine (T/N) in cigarettes smoked

	Males	Females
High T/N[1]	1.00	1.00
Medium T/N	0.95	0.79
Low T/N	0.81	0.60

[1]The mortality rate for the category with highest risk was made 1.00 so that the relative reductions in risk with the use of lower T/N cigarettes could be visualized.

Source: U.S. DHHS, 1982.

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Source: https://www.industrydocuments.ucsf.edu/docs/rsdl0000

Table 4-9. Relative risk for lung cancer by type of cigarette smoked (filter vs. nonfilter), in men, based on cohort and case-control studies

Reference	Type of study	Relative risk
Hawthorne & Fry (1978)	Cohort	0.8
Rimington (1981)	Cohort	0.7
Bross & Gibson (1968)	Case-control	0.6
Wynder et al. (1970)	Case-control	0.6
Dean et al. (1977)	Case-control	0.5

Source: IARC, 1986.

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Source: https://www.industrydocuments.ucsf.edu/docs/rsdl0000

Table 4-10. Main results of studies dealing with the relationship between smoking and different histological types of lung cancer

Reference	Histological type	Results						Comments
Doll et al. (1957)		Sex	No. of Cases	Relative Risk				Nonsmokers, 1.0 (RR) No. observed
				Amount of Tobacco Smoked (g)				
				<5	5-14	15-24	25+	
	Kreyberg I	M	829	4.7	10.6	14.3	25.4	3
		F	32	1.0	1.7	8.3		16
	Kreyberg II	M	38	0.5	0.8	1.2	1.1	2
		F	8	1.1	2.3	4.1		5
Hammond & Horn (1958b)		Relative risk no. of packs/day						Nonsmokers, 1.0 Only regular smokers considered
		<½		½-1		1+		
	Adenocarcinoma	2.0		2.5		7.0		
	Other types	16.3		25.5		88.0		
Doll & Hill (1964a)		Death Rate/1000 Amount of tobacco smoked						Men only
		Ex-Smokers		1-14g	15-24g	25+g		
	Squamous-cell carcinoma	0.09		0.22	0.33	0.45		
	Small-cell and anaplastic carcinoma	0.05		0.10	0.20	0.38		
	Adenocarcinoma	0.03		0.03	0.12	0.07		

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Table 4-10. (continued)

Reference	Histological Type	Results					Comments
Haenszel & Taeuber (1964)		Standardized mortality ratio					Women only; standardized mortality ratio; total group, 1.00
		Never smoked	Ex-smokers	Occasional cigarette Smokers	Regular cigarette smokers <1 pack/day	Regular cigarette smokers >1 pack/day	
	Adenocarcinoma	0.78	0.35	2.46	1.17	7.50	
	Squamous-cell and undifferentiated carcinoma	0.59	0.52	1.15	2.19	8.78	
Hanbury (1964)		No. of cases (%)					Women only
		"Heavy" and "medium" smokers		Nonsmokers and "Remainder"			
	Small-cell carcinoma	18 (47)		21 (34)			
	Undifferentiated carcinoma	9 (24)		14 (23)			
	Squamous-cell carcinoma	9 (24)		12 (19)			
	Adenocarcinoma	2 (5)		15 (24)			

Vincent, T.N. et al. (1965)	Total no. of cases	Number of cigarettes smoked/day										Women only
		None		1-20		21-40		41+		Unknown		
		No.	%	No.	%	No.	%	No.	%	No.	%	
Squamous-cell	19	10	53	3	16	2	10	2	10	2	10	
carcinoma	17	2	12	7	41	6	35	2	12	0	0	
Small-cell carcinoma	64	51	80	6	9	4	6	0	0	3	5	
Adenocarcinoma	22	12	54	4	18	6	27	0	0	0	0	
Undifferentiated	41	32	78	8	20	1	2	0	0	0	0	
Others	163	107	66	28	17	19	12	4	2	5	3	

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Table 4-10. (continued)

Reference	Histological Type	Results			Comments
Deaner & Trummer (1979)		Pack-years	Number of Tumors	Smokers	
	Undifferentiated carcinoma	40	40	40 (100%)	
	Adenocarcinoma	12	19	13 (68%)	
	Squamous-cell carcinoma	52	9	9 (100%)	
Wynder et al. (1970)		Sex	No.(%)		Heavy = 41+ cigarettes/day
			Cigarette Smokers	Heavy Smokers	
	Kreyberg I	M	191 (91.0)	59 (29.9)	
		F	24 (80.0)	3 (12.0)	
	Kreyberg II	M	61 (82.4)	9 (14.1)	
		F	21 (58.3)	1 (4.8)	
	Controls	M	199 (47.4)	26 (9.8)	
		F	53 (40.2)	3 (5.4)	
Weiss, W. et al. (1972)		Death rate per 1,000 man-years of observation (adjusted for age and race) No. of cigarettes/day			
		1-10	10-19	20+	
	Squamous-cell carcinoma	-	0.8	2.1	
	Well differentiated	0.7	0.4	1.0	
	Poorly differentiated	-	0.3	0.7	
	Small-cell carcinoma	-	0.6	1.0	
	Adenocarcinoma				

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Table 4-10. (continued)

Reference	Histological Type	Result					Comments
Vincent, R.G. et al. (1977)		No. of Cigarettes Smoked/Day					
		0	1-20	21-40	41+	Other	
	Squamous-cell carcinoma	14	219	110	120	16	
	Adenocarcinoma	28	101	66	53	7	
	Small-cell carcinoma	4	103	62	56	6	
	Large-cell carcinoma	2	40	32	33	0	
	Bronchiolo-alveolar carcinoma	6	20	9	6	0	
	Mixed	0	9	5	5	0	
	Other	6	30	19	17	4	

Reference	Histological Type	Result							Comments
Chan et al. (1979)		Smoking Category (kg Tobacco Smoked During Lifetime)							Women only
		Non-smokers	≤100		100-199		>200		
			Manufac-tured	All	Manufac-tured	All	Manufac-tured	All	
	Squamous-cell and small-cell carcinomas	1.0	3.6	3.4	3.7	4.2	2.6	4.1	
	Adenocarcinoma	1.0	1.9	1.4	1.4	1.8	1.6	1.7	

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Table 4-10. (continued)

Joly, O.G. et al. (1983)	Relative Risk by Duration of Smoking (Years)								Nonsmokers, 1.0
	Men				Women				
	1-29	30-39	40-49	50+	1-29	30-39	40-49	50+	
Squamous-cell carcinoma	15.0	15.9	39.5	42.2	4.4	9.4	31.4	51.9	
Adenocarcinoma	2.0	3.2	5.3	5.7	2.1	2.7	4.7	4.0	
Undifferentiated carcinoma	26.0	26.4	40.7	50.0	3.9	15.6	20.6	28.3	
Poorly differentiated carcinoma	6.4	7.7	10.8	10.2	3.2	7.8	5.6	13.1	

Source: IARC, 1986.

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Table 4-11. Lung cancer death attributable to tobacco smoking in certain countries

Country	Year	No. of Deaths[1]	Expected Deaths in Nonsmokers[2]	Crude Rate in Persons Aged 35+ Observed	In Non-Smokers	AC[3]	AP[4]
Canada							
Men	1978	6,435	556	142.8	11.8	5,762	0.9
Women	1978	1,681	487	34.0	9.9	1,194	0.71
England & Wales							
Men	1981	26,297	1,576	228.5	13.3	24,720	0.94
Women	1981	8,430	1,663	63.3	12.4	6,767	0.80
Japan							
Men	1981	16,638	2,868	64.8	10.7	13,184	0.83
Women	1981	6,161	2,593	21.0	8.9	3,568	0.58
Sweden							
Men	1981	1,777	301	85.0	14.0	1,476	0.83
Women	1981	654	281	28.0	12.3	373	0.57
USA							
Men	1979	72,803	5,778	166.7	12.7	67,024	0.92
Women	1979	25,648	5,736	50.0	11.1	19,912	0.78

[1]From the Global Epidemiological Surveillance and Health Situation Assessment data bank of WHO.
[2]Calculated by IARC, 1986. Slightly overestimates number of expected deaths.
[3]AC, number of cases attributable to smoking.
[4]AP, proportion of cases attributable to smoking.

Source: IARC, 1986.

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Source: https://www.industrydocuments.ucsf.edu/docs/rsdl0000

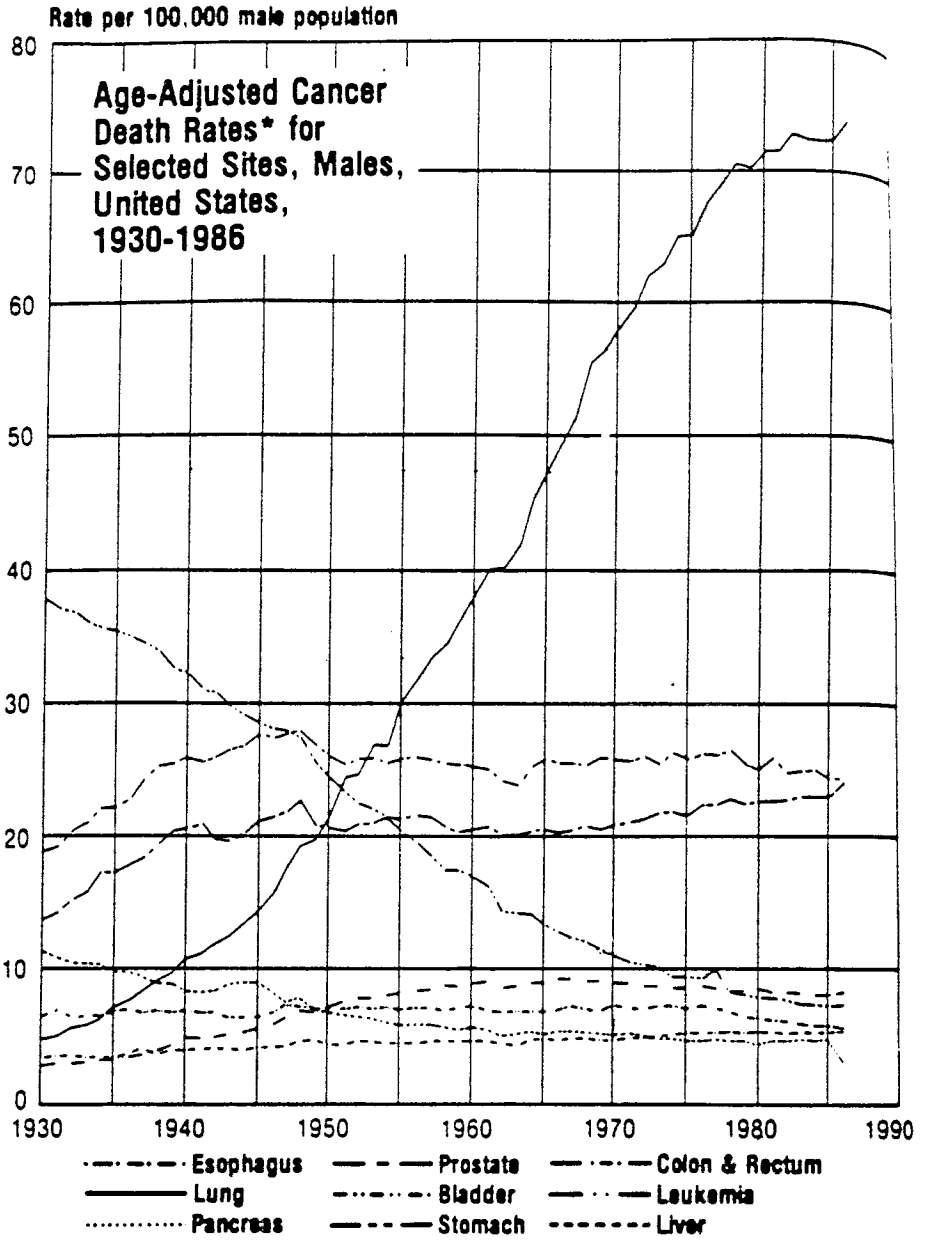

Figure 4-1. Age-adjusted cancer death rates* for selected sites, males, United States, 1930-1986.

*Adjusted to the age distribution of the 1970 U.S. census population.

Source: U.S. DHHS, 1989.

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Source: https://www.industrydocuments.ucsf.edu/docs/rsdl0000

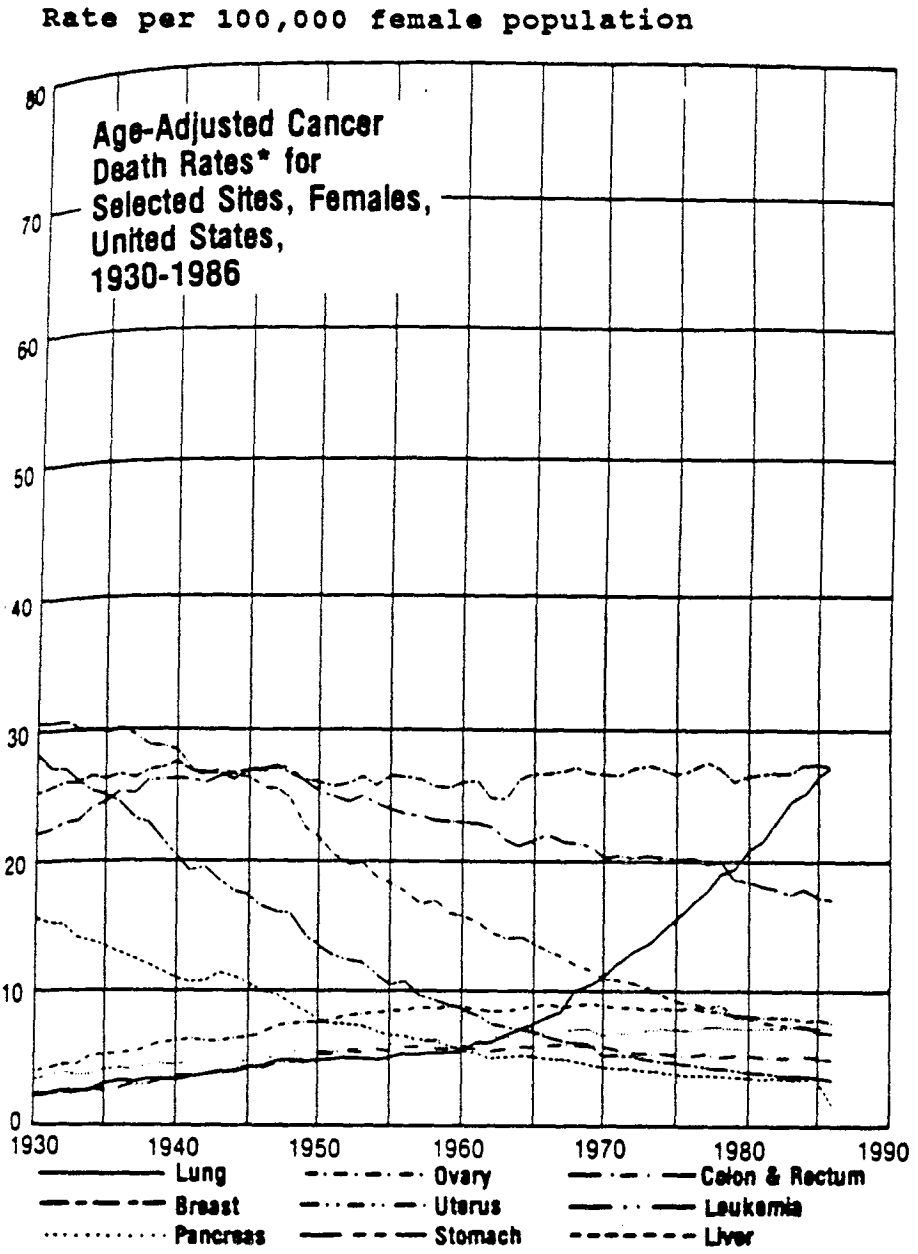

Figure 4-2. Age-adjusted cancer death rates* for selected sites, females, United States, 1930-1986.

*Adjusted to the age distribution of the 1970 U.S. census population.

Source: U.S. DHHS, 1989.

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Source: https://www.industrydocuments.ucsf.edu/docs/rsdl0000

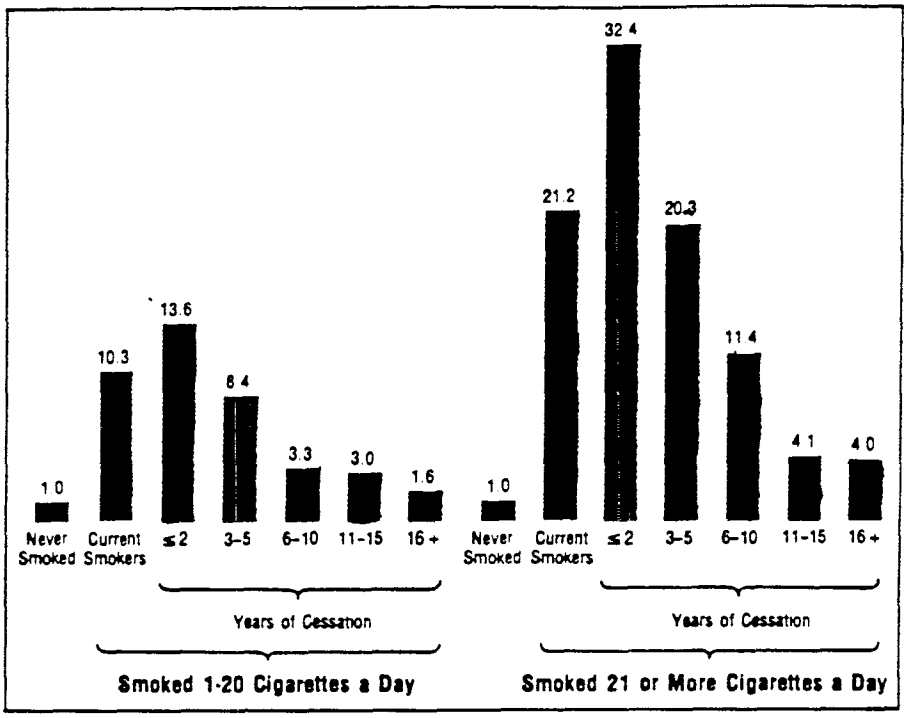

Figure 4-3. Relative risk of lung cancer in ex-smokers, by number of years quit, women, Cancer Prevention Study II

Source: Garfinkel and Silverberg, 1991.

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Source: https://www.industrydocuments.ucsf.edu/docs/rsdl0000